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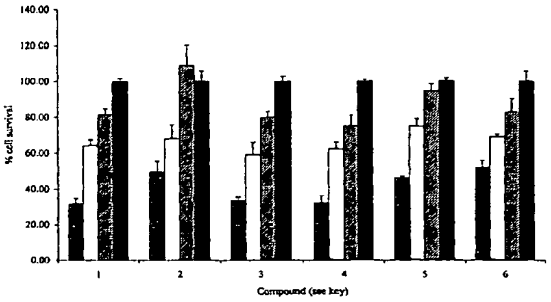
(54) Title: NEW USE

(57) Abstract: The present invention provides the use of a low molecular weight mammalian AP endonuclease inhibitor for the preparation of a medicament for the treatment of cancer.



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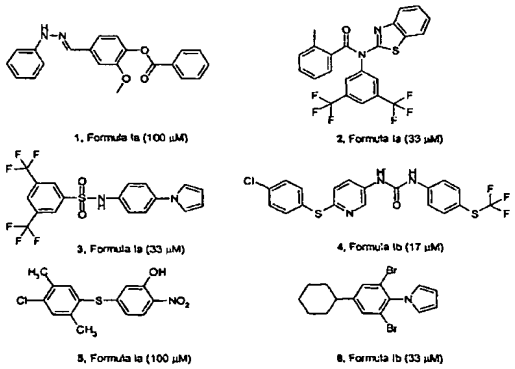

Solid black bars – Cells only. Hatched bars – Cells plus compound only. Open bars – Cells plus MMS only. Solid grey bars – cells plus compounds and MMS.

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NEW USE

Field of the Invention

This invention relates to the use of compounds in the treatment of cancer.

Background and Prior Art

One of the most common lesions generated in DNA is the apurinic/apyrimidinic (AP) site, which results from the hydrolysis of the *N*-glycosyl bond linking the base to the deoxyribose moiety. AP sites can arise either through spontaneous hydrolysis (see Lindahl, T. *Mutat. Res.* 238, 305-311 (**1990**) and Lindahl, T. *Nature* 362, 709-715 (**1993**)), as a result of DNA glycosylase activity within the base excision repair pathway, or as a result of base damage caused by DNA damaging drugs or ionising radiation. These abasic sites disrupt DNA replication and are highly mutagenic if not repaired.

All cells express repair enzymes to remove the AP sites. AP endonucleases are classified into two families according to their homology to *E. coli* endonucleases: exonuclease III (xth) and endonuclease IV (nfo). The first of these families derives from organisms across several phyla, including ExoIII (*E. coli*), Exo A (*Streptococcus pneumoniae*), Rrp 1 (*Drosophila melanogaster*), Arp (*Arabidopsis thaliana*), Apn2 (*S. cerevisiae*), APEX (mouse), BAP1 (bovine), rAPE (rat) and chAPE1 (hamster).

The major AP endonuclease in human cells is termed HAP1 (also known as Ape1 and Ref-1), which is a multi-functional enzyme that, as well as being involved in the repair of AP sites, functions as a redox factor, maintaining

numerous transcription factors in an active state (for a review see Evans, A.R. *et al. Mutation Research* 461, 83-108 (**2000**)).

Along with the other enzymes having homology to Exo III, HAP1 exhibits strong AP hydrolytic activity. Repair catalysed by HAP1 is generally initiated by endonucleolytic cleavage 5' to the abasic region. Furthermore, HAP1 is a multifunctional enzyme that also possesses 3' phosphodiesterase and RNase H activities. These activities are catalysed at a single active site (see Barzilay, G. *et al. Nature Structural Biology* 2(7), 561-567 (**1995**)).

AP endonucleases such as HAP1 play extremely important roles in cell maintenance. Indeed, it is reported in US Patent No. 6,190,661 that decreased amounts of HAP1 are present in cells that are undergoing or are likely to undergo programmed cell death (apoptosis).

The role that is played by HAP1 means that it is a potentially important target for new cancer therapies. Indeed, it is reported that elevated expression of HAP1 in NT2 cells confers resistance to both bleomycin and radiation (see Robertson, K. A. *et al. Cancer Res.* 61, 2220-2225 (**2001**)). It is also known that nuclear expression of HAP1 in head-and-neck cancer is associated with resistance to chemoradiotherapy (see Koukourakis, M. D. *et al. Int. J. Radiation Oncology Biol. Phys.* 50(1), 27-36 (**2001**)).

In this respect, US 6,190,661 discloses that reduction of HAP1 activity may be used to (a) treat HAP1-related premalignant or malignant conditions, (b) induce apoptosis in a cell and (c) enhance the sensitivity of the cells of HAP1-related malignancy or premalignancy to chemotherapy, radiotherapy or gene therapy. The methods for reducing HAP1 activity that are disclosed in US 6,190,661 include inhibiting expression of HAP1 or inhibiting the function of HAP1. Furthermore, Grafström *et al.* (see Abstract number C5-

121 "*AP Endonuclease: A Possible Target for a Novel Tumoricidal Compound*" Repair and Processing of DNA Damage, Taos, NM, 23rd to 29th March 1995) disclose the use of compounds that inhibit HAP1, as well as cleave AP sites in DNA, in the treatment of cancer.

Nevertheless, as far as the inventors are aware no one has previously disclosed the use of compounds that do not cleave AP sites in DNA as low molecular weight mammalian AP endonuclease inhibitors, or the use of such inhibitors in the treatment of cancer.

Disclosure of the Invention

According to a first aspect of the invention there is provided the use of a low molecular weight mammalian AP endonuclease inhibitor, which inhibitor does not cleave AP sites in DNA, for the preparation of a medicament for the treatment of cancer.

When used herein, the term "low molecular weight" includes compounds having a molecular weight of below 5000 g/mole, such as below 4000 g/mole (e.g. below 3000 g/mole), and particularly compounds having a molecular weight below 2500 g/mole (e.g. below 1500, 1200, 1000, 900 or, especially, 800 g/mole).

When used herein, the term "mammalian AP endonuclease inhibitor" includes compounds that inhibit any function of mammalian AP endonuclease enzymes, such as exo- and/or endonuclease activity (particularly the endonuclease activity). AP endonuclease enzymes that may be inhibited include APEX, BAP1, rAPE, chAPE1, Ape2, hNTH1 and, particularly, HAP1.

Inhibition of the activity of mammalian AP endonuclease enzymes may be determined by any suitable assay, for example the assay described in Barzilay, G. *et al. Nature Structural Biology* 2(7), 561-567 (1995), the disclosures of which document are hereby incorporated by reference.

Preferred mammalian AP endonuclease inhibitors include compounds that inhibit the function of a mammalian AP endonuclease enzyme at a concentration of 50 μmoles/L or below. Preferred mammalian AP endonuclease inhibitors also include compounds that inhibit the function of mammalian AP endonuclease enzymes selectively over other endonuclease enzymes. Such selective inhibitors include compounds that, at the same concentration, are at least twice as effective (e.g. at least four times as effective) at inhibiting the function of a mammalian AP endonuclease enzyme (e.g. HAP1) as they are at inhibiting the function of other endonuclease enzymes (e.g. the restriction enzyme HpaII).

Preferred low molecular weight mammalian AP endonuclease inhibitors include low molecular weight inhibitors of HAP1.

When used herein, the term "which inhibitor does not cleave AP sites in DNA" includes inhibitors that, when brought into contact (e.g. admixed in aqueous solution) with DNA that contains at least one AP site, do not promote or cause scission of the phosphodiester backbone at the AP site(s) (e.g. by a β-elimination mechanism).

According to a second aspect of the invention there is provided the use of a compound of formula I,

$$R^1—Ar^1—X—Ar^2—R^2 \qquad I$$

wherein Ar^1 represents aryl;

Ar^2 represents phenyl or Het^1;

Het^1 represents a wholly aromatic or part-aromatic five- to fourteen-membered heterocyclic group containing one or more heteroatoms selected from O, N and S;

R^1 and R^2 independently represent one or more optional substituents on Ar^1 and Ar^2, respectively, which substituents are selected from halo, nitro, cyano, OR^3, SR^4, $N(R^5)R^6$, aryl, Het^2, $C(O)R^7$, $C(R^{7a})=N\text{-}OR^{7b}$, $C(R^{7a})=N\text{-}N(H)R^{7b}$, $C(O)OR^8$, $C(O)N(R^9)R^{10}$, $S(O)_nR^{11}$ and $C_{1\text{-}12}$ alkyl (which latter group is optionally substituted and/or terminated by one or more substituents selected from halo, aryl, cyano and $N(R^{5a})R^{6a}$);

R^3 and R^4 independently represent H, $C_{1\text{-}12}$ alkyl (optionally substituted and/or terminated by one or more substituents selected from halo and aryl), aryl, Het^3 or $C(O)R^{12a}$ or R^3 represents SO_2(aryl);

R^5 and R^6 independently represent H, $C_{1\text{-}12}$ alkyl (optionally substituted and/or terminated by one or more substituents selected from halo and aryl), aryl, Het^4, $C(O)R^{12b}$, $C(O)N(R^{12c})R^{12d}$, $C(O)OR^{12d}$ or SO_2(aryl), or R^5 represents $N=C(R^{5b})(R^{6b})$;

R^{5a} and R^{6a} independently represent H or $C_{1\text{-}6}$ alkyl;

R^{5b} and R^{6b} independently represent H or $C_{1\text{-}6}$ alkyl, or R^{5b} and R^{6b}, together with the C-atom to which they are attached, form a 5- to 10-membered, monocyclic or bicyclic, fully saturated or partly aromatic, heterocyclic or carbocyclic ring system, wherein, when the ring system is heterocyclic, it contains one to three heteroatoms selected from O, N and S, and wherein the carbocyclic or heterocyclic ring system is optionally substituted by one or more substituents selected from halo, cyano, =O and $C_{1\text{-}6}$ alkyl;

R^7 and R^8 independently represent H, $C_{1\text{-}12}$ alkyl (optionally substituted and/or terminated by one or more substituents selected from halo and aryl), aryl or Het^5;

R^{7a} represents, at each occurrence, H or $C_{1\text{-}6}$ alkyl;

R^{7b} represents, at each occurrence, C_{1-6} alkyl, aryl, Het^5, $C(O)R^{7c}$, $C(O)OR^{7d}$ or $C(O)N(R^{7e})R^{7f}$;

R^{7c} to R^{7f} independently represent C_{1-6} alkyl (optionally substituted by one or more substituents selected from halo, aryl and adamantyl), aryl or Het^5, or R^{7e} represents H;

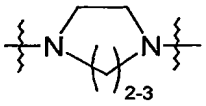
R^9 represents H, C_{1-12} alkyl (optionally substituted and/or terminated by one or more substituents selected from halo and aryl), aryl, Het^6 or $N(H)C(O)R^{12e}$;

R^{11} represents C_{1-12} alkyl (optionally substituted and/or terminated by one or more substituents selected from halo and aryl), aryl or Het^7;

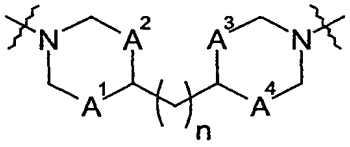
n represents 1 or 2;

R^{10} and R^{12a} to R^{12e} independently represent H, C_{1-6} alkyl (optionally substituted and/or terminated by one or more substituents selected from halo and aryl), aryl or Het^8;

X represents a direct bond linking Ar^1 to Ar^2, the structural fragment



or the structural fragment



wherein the wavy lines indicates the bond positions of the fragment;

A^1 to A^4 independently represent a direct bond or CH_2; and

n represents 1 to 4;

or X represents the group A-D;

wherein A represents O, S, S(O), $S(O)_2$, $N(R^{13})$, C(O), CH(OH) or $C(R^{13a})$=; and

when A represents O, then D represents a direct bond, $S(O)_2$, $P(O)(OR^{14a})O$, C(O), C(S), C(O)O, $C(O)N(R^{15a})$ or $CH_2C(O)$;

when A represents S, then D represents a direct bond, C(O), C(S), C(O)O, $C(O)N(R^{15b})$, $CH_2C(O)NHNHC(S)NH$ or $CH_2C(O)$;

when A represents S(O) or $S(O)_2$, then D represents a direct bond or $CH_2C(O)$;

when A represents $N(R^{13})$, then D represents a direct bond, $N(R^{13b})$, $S(O)_2$, C(O), C(S), $C(O)C(R^{13c})(R^{13d})$, $C(O)N(R^{15c})$, $C(S)N(R^{15d})$, $C(S)N(H)N=C(R^{13e})$, $N=C(R^{14b})$- or $CH_2C(O)$;

when A represents C(O), then D represents a direct bond, $N(R^{15e})N(R^{15f})$, $N(R^{15g})N=C(R^{14c})$-, $N(R^{15h})N(R^{15i})C(O)$, $N(R^{15j})C(O)N(R^{15k})$ or $N(R^{16})C(R^{17})=N$-;

when A represents CH(OH), then D represents a direct bond;

when A represents $C(R^{13a})=$, then D represents $NN(H)C(O)N(H)N=C(R^{13f})$, N-O, N-OC(O), N-OC(O)O or $N\text{-}OC(O)N(R^{13g})$;

R^{13} represents H, C_{1-6} alkyl, aryl or Het^9;

R^{13a} to R^{13g} independently represent H or C_{1-6} alkyl;

R^{14a} to R^{14c} independently represent C_{1-6} alkyl or aryl, or R^{14b} and R^{14c} independently represent H;

R^{15a} to R^{15k} independently represent H, C_{1-6} alkyl, aryl or Het^{10};

R^{16} represents H, C_{1-6} alkyl, aryl or R^{16}, together with R^{17} and the N- and C-atoms to which those groups are attached, form a four- to seven-membered heterocyclic group containing at least one nitrogen atom (the atom to which R^{16} is attached) and optionally containing one or more further heteroatoms selected from O, N and S, which heterocyclic group is optionally unsaturated and/or substituted by one or more groups selected from OH, halo, cyano, nitro, C_{1-4} alkyl, C_{1-4} alkoxy, $=C(R^{18})R^{19}$ and *spiro*-$(CH_2)_p$;

R^{17} represents H, $C(R^{20a})(R^{20b})R^{20c}$, OR^{20d}, SR^{20e} or $N(R^{20f})R^{20g}$ or R^{17}, together with R^{16} and the N- and C-atoms to which those groups are attached, form a four- to seven-membered heterocyclic group containing at least one nitrogen atom (the atom to which R^{16} is attached) and optionally containing one or more further heteroatoms selected from O, N or S, which heterocyclic group is optionally unsaturated and/or substituted by one or more groups selected from OH, halo, cyano, nitro, C_{1-4} alkyl, C_{1-4} alkoxy, $=C(R^{18})R^{19}$ and *spiro*-$(CH_2)_p$;

R^{18} and R^{19} independently represent H, C_{1-4} alkyl or aryl;

p represents 3 to 6;

R^{20a} to R^{20g} independently represent C_{1-6} alkyl, aryl or Het^{11} or R^{20a} to R^{20c} independently represent H;

Het^2 to Het^{11} independently represent, at each occurrence when used herein, four- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from O, N and S, which heterocyclic groups are optionally substituted by one or more substituents selected from =O, $-OR^{21a}$, $S(O)_qR^{21b}$, cyano, halo, nitro, C_{1-6} alkyl, aryl, $-N(R^{21c})R^{21d}$, $-C(O)R^{21e}$, $-C(O)OR^{21f}$, $-C(O)N(R^{21g})R^{21h}$, $-N(R^{21i})C(O)R^{21j}$, $-N(R^{21k})C(O)N(R^{21m})R^{21n}$ and $-N(R^{21o})S(O)_2R^{21p}$;

R^{21a} to R^{21p} independently represent H, C_{1-6} alkyl or aryl, provided that R^{21b} does not represent H when q represents 1 or 2; and

q represents 0, 1 or 2;

wherein each aryl or phenyl group, unless otherwise specified, is optionally substituted;

or a pharmaceutically acceptable derivative thereof;

for the preparation of a medicament for the treatment of cancer.

For the avoidance of doubt, in compounds of formula I, the group A may be attached either to the group Ar^1 or to the group Ar^2.

Unless otherwise specified, alkyl groups and alkoxy groups as defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of three) of carbon atoms, be branched-chain and/or cyclic. Further, when there is a sufficient number (i.e. a minimum of four) of carbon atoms, such alkyl and alkoxy groups may also be part cyclic/acyclic. Such alkyl and alkoxy groups may also be saturated or, when there is a sufficient number (i.e. a minimum of two) of carbon atoms, be unsaturated and/or interrupted by one or more oxygen and/or sulfur atoms. Unless otherwise specified, alkyl and alkoxy groups may also be substituted by one or more halo, and especially fluoro, atoms.

The term "aryl", when used herein, includes C_{6-10} aryl groups such as phenyl, naphthyl and the like. Unless otherwise specified, aryl and phenyl groups may be substituted by one or more substituents including $-OR^{21a}$, $S(O)_qR^{21b}$, cyano, halo, nitro, C_{1-6} alkyl, $-N(R^{21c})R^{21d}$, $-C(O)R^{21e}$, $-C(O)OR^{21f}$, $-C(O)N(R^{21g})R^{21h}$, $-N(R^{21i})C(O)R^{21j}$, $-N(R^{21k})C(O)N(R^{21m})R^{21n}$ and $-N(R^{21o})S(O)_2R^{21p}$, wherein R^{21a} to R^{21p}, p and alkyl are as hereinbefore defined. When substituted, aryl and phenyl groups are preferably

substituted by one to three substituents. When an aryl or phenyl group is substituted by one or more substituents that contain(s) (a) further aryl group(s), then the further aryl group(s) may not itself (themselves) be substituted by any substituent that contains one or more aryl groups.

Substituents on aryl and phenyl groups that may be mentioned include one or more substituents selected from $-OR^{21a}$, $S(O)_qR^{21b}$, cyano, halo, nitro, C_{1-6} alkyl, $-N(R^{21c})R^{21d}$, $-C(O)R^{21e}$, $-C(O)OR^{21f}$, $-C(O)N(R^{21g})R^{21h}$, $-N(R^{21i})C(O)R^{21j}$ and $-N(R^{21k})C(O)N(R^{21m})R^{21n}$, wherein R^{21a} to R^{21n}, p, q and alkyl are as hereinbefore defined.

However, further substituents on aryl and phenyl groups that may be mentioned include one or more substituents selected from at least one $-N(R^{21o})S(O)_2R^{21p}$ group and, if appropriate, one or more further groups selected from $-OR^{21a}$, $S(O)_qR^{21b}$, cyano, halo, nitro, C_{1-6} alkyl, $-N(R^{21c})R^{21d}$, $-C(O)R^{21e}$, $-C(O)OR^{21f}$, $-C(O)N(R^{21g})R^{21h}$, $-N(R^{21i})C(O)R^{21j}$, $-N(R^{21k})C(O)N(R^{21m})R^{21n}$ and $-N(R^{21o})S(O)_2R^{21p}$, wherein R^{21a} to R^{21p}, p, q and alkyl are as hereinbefore defined.

The term "halo", when used herein, includes fluoro, chloro, bromo and iodo.

Het^1 groups that may be mentioned include those containing 1 to 4 heteroatoms (selected from the group oxygen, nitrogen and/or sulfur) and in which the total number of atoms in the ring system are between five and twelve. Het^1 groups may be mono- or bicyclic in character. Heterocyclic groups that may be mentioned in relation to Het^1 include those mentioned in relation to Het^2 to Het^{11} below. Values of Het^1 that may be mentioned include 1,5-dihydro-benzo[e][1,3]dithiepinyl, benzimidazolyl, benzofuranyl, benzothiazolyl, benzothiophenyl, indolyl, isoxazolyl, oxadiazolyl, pyridinyl, pyrrolyl, quinolinyl, tetrazolyl, thiazolyl and thienyl.

Het^2 to Het^{11} groups that may be mentioned include those containing 1 to 4 heteroatoms (selected from the group oxygen, nitrogen and/or sulfur) and in which the total number of atoms in the ring system are between five and twelve. Het^2 to Het^{11} groups may be fully saturated, partly unsaturated, wholly aromatic, partly aromatic and/or bicyclic in character. Heterocyclic groups that may be mentioned in relation to Het^2 to Het^{11} include benzodioxanyl, benzodioxepanyl, benzodioxolyl, benzofuranyl, benzofurazanyl, benzimidazolyl, benzomorpholinyl, benzothiazolyl, benzothiophenyl, benzoxazinonyl, chromanyl, chromenonyl, cinnolinyl, dihydroquinazolinonyl, dioxanyl, furanyl, hydantoinyl, imidazolyl, imidazo[1,2-*a*]pyridinyl, indolyl, isoquinolinyl, isoxazolyl, maleimido, morpholinyl, oxazolyl, phthalazinyl, piperazinyl, piperidinyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridinyl, pyrimindinyl, pyrrolidinonyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 3-sulfolenyl, tetrahydropyranyl, tetrahydrofuranyl, thiadiazolyl, thiazolyl, thienyl, thiochromanyl, triazolyl and the like. Values of Het^2 that may be mentioned include benzimidazolyl, benzoxazinonyl, chromenonyl, piperidinyl, pyrazolyl, pyrrolyl, thiadiazolyl and thienyl. Values of Het^3 that may be mentioned include pyridinyl and thienyl. Values of Het^5 that may be mentioned include dihydroquinazolinonyl. Values of Het^6 and Het^7 that may be mentioned include benzothiazolyl. Values of Het^8 that may be mentioned include isoxazolyl and furanyl. Values of Het^9 that may be mentioned include benzothiazolyl.

Substituents on Het (Het^1 to Het^{11}) groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point of attachment of Het (Het^1 to Het^{11}) groups may be *via* any atom in the ring system including (where appropriate) a heteroatom, or an atom on any fused

carbocyclic ring that may be present as part of the ring system. Het (Het^1 to Het^{11}) groups may also be in the *N*- or *S*-oxidised form.

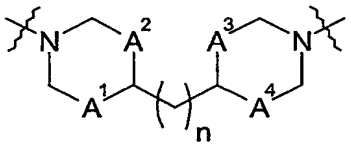
Compounds of formula I that may be mentioned include those in which:

Het^1 represents a wholly aromatic or part-aromatic five- to twelve-membered heterocyclic group containing one or more heteroatoms selected from O, N and S;

R^1 and R^2 independently represent one or more optional substituents on Ar^1 and Ar^2, respectively, which substituents are selected from halo, nitro, cyano, OR^3, SR^4, $N(R^5)R^6$, aryl, Het^2, $C(O)R^7$, $C(O)OR^8$, $C(O)N(R^9)R^{10}$, $S(O)_nR^{11}$ and C_{1-12} alkyl (which latter group is optionally substituted and/or terminated by one or more substituents selected from halo, aryl, cyano and $N(R^{5a})R^{6a}$);

R^5 and R^6 independently represent H, C_{1-12} alkyl (optionally substituted and/or terminated by one or more substituents selected from halo and aryl), aryl, Het^4, $C(O)R^{12b}$, $C(O)N(R^{12c})R^{12d}$, $C(O)OR^{12d}$ or SO_2(aryl);

X represents a direct bond linking Ar^1 to Ar^2, the structural fragment



wherein the wavy lines indicates the bond positions of the fragment;

or X represents the group A-D;

wherein A represents O, S, S(O), $S(O)_2$, $N(R^{13})$, C(O) or $C(R^{13a})$=; and

when A represents O, then D represents a direct bond, $S(O)_2$, $P(O)(OR^{14a})O$, C(O), C(S), C(O)O or $C(O)N(R^{15a})$;

when A represents S, then D represents a direct bond, C(O), C(S), C(O)O, $C(O)N(R^{15b})$ or $CH_2C(O)NHNHC(S)NH$;

when A represents S(O) or $S(O)_2$, then D represents a direct bond;

when A represents $N(R^{13})$, then D represents a direct bond, $N(R^{13b})$, $S(O)_2$, C(O), C(S), $C(O)C(R^{13c})(R^{13d})$, $C(O)N(R^{15c})$, $C(S)N(R^{15d})$, $C(S)N(H)N=C(R^{13e})$ or $N=C(R^{14b})$-;

when A represents C(O), then D represents a direct bond, $N(R^{15e})N(R^{15f})$, $N(R^{15g})N=C(R^{14c})$-, $N(R^{15h})N(R^{15i})C(O)$ or $N(R^{16})C(R^{17})=N$-;

when A represents $C(R^{13a})=$, then D represents $NN(H)C(O)N(H)N=C(R^{13f})$;

Het^2 to Het^{11} independently represent four- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from O, N and S, which heterocyclic groups are optionally substituted by one or more substituents selected from =O, $-OR^{21a}$, $S(O)_qR^{21b}$, cyano, halo, nitro, C_{1-6} alkyl, aryl, $-N(R^{21c})R^{21d}$, $-C(O)R^{21e}$, $-C(O)OR^{21f}$, $-C(O)N(R^{21g})R^{21h}$, $-N(R^{21i})C(O)R^{21j}$ and $-N(R^{21k})C(O)N(R^{21m})R^{21n}$;

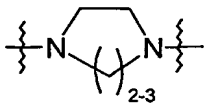
Further compounds of formula I that may be mentioned include those in which at least one of the following applies:

(i) Het^1 represents a wholly aromatic or part-aromatic thirteen- or fourteen-membered heterocyclic group containing one or more heteroatoms selected from O, N and S;

(ii) R^1 and R^2 independently represent one or more substituents on Ar^1 and Ar^2, respectively, which substituents are selected from at least one $C(R^{7a})=N\text{-}OR^{7b}$ or $C(R^{7a})=N\text{-}N(H)R^{7b}$ group and, if appropriate, one or more further groups selected from halo, nitro, cyano, OR^3, SR^4, $N(R^5)R^6$, aryl, Het^2, $C(O)R^7$, $C(R^{7a})=N\text{-}OR^{7b}$, $C(R^{7a})=N\text{-}N(H)R^{7b}$, $C(O)OR^8$, $C(O)N(R^9)R^{10}$, $S(O)_nR^{11}$ and C_{1-12} alkyl (which latter group is optionally substituted and/or terminated by one or more substituents selected from halo, aryl, cyano and $N(R^{5a})R^{6a}$);

(iii) R^5 represents $N=C(R^{5b})(R^{6b})$;

(iv) X represents the structural fragment



;

(v) A represents CH(OH);

(vi) when A represents O, S, S(O), $S(O)_2$ or $N(R^{13})$, then D represents $CH_2C(O)$;

(vii) when A represents C(O), then D represents $N(R^{15j})C(O)N(R^{15k})$;

(viii) when A represents $C(R^{13a})=$, then D represents N-O, N-OC(O), N-OC(O)O or $N\text{-}OC(O)N(R^{13g})$;

(ix) Het^2 to Het^{11} independently represent, at each occurrence when used herein, four- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from O, N and S, which heterocyclic groups are substituted by a $-N(R^{21o})S(O)_2R^{21p}$ group and which heterocyclic groups are optionally substituted by one or more further substituents selected from =O, $-OR^{21a}$, $S(O)_qR^{21b}$, cyano, halo, nitro, C_{1-6} alkyl, aryl, $-N(R^{21c})R^{21d}$, $-C(O)R^{21e}$, $-C(O)OR^{21f}$, $-C(O)N(R^{21g})R^{21h}$, $-N(R^{21i})C(O)R^{21j}$, $-N(R^{21k})C(O)N(R^{21m})R^{21n}$ and $-N(R^{21o})S(O)_2R^{21p}$.

Preferred compounds of formula I include those in which:

Ar^1 represents phenyl;

Het^1 represents a wholly aromatic or part-aromatic five- to twelve-membered heterocyclic group containing one to four heteroatoms selected from O, N and S;

R^1 and R^2 independently represent one or more optional substituents on Ar^1 and Ar^2, respectively, which substituents are selected from halo, nitro, cyano, OR^3, SR^4, $N(R^5)R^6$, optionally substituted phenyl, Het^2, $C(O)R^7$, $C(O)OR^8$, $C(O)N(R^9)R^{10}$, $S(O)_2$(optionally substituted phenyl) and C_{1-8} alkyl (which latter group is optionally unsaturated and/or substituted and/or

terminated by one or more substituents selected from halo, cyano, $N(R^{5a})R^{6a}$ and optionally substituted phenyl);

R^3 and R^4 independently represent H, C_{1-8} alkyl (optionally substituted and/or terminated by one or more substituents selected from halo and phenyl, which latter group is optionally substituted), Het^3, optionally substituted phenyl or $C(O)R^{12a}$ or R^3 represents $S(O)_2$(optionally substituted phenyl);

R^5 and R^6 independently represent H, C_{1-6} alkyl, optionally substituted phenyl, $C(O)R^{12b}$ or $S(O)_2$(optionally substituted phenyl);

R^{5a} and R^{6a} independently represent H or C_{1-2} alkyl;

R^7 and R^8 independently represent H, C_{1-6} alkyl, Het^5 or optionally substituted phenyl;

R^9 represents H, C_{1-6} alkyl, optionally substituted phenyl, Het^6 or $N(H)C(O)R^{12e}$;

R^{10}, R^{12a}, R^{12b} and R^{12e} independently represent H, C_{1-4} alkyl, optionally substituted phenyl or Het^8;

A^1 to A^4 all represent CH_2;

n represents 3 or 4;

when A represents O, then D represents a direct bond, $S(O)_2$, C(O) or C(O)N(H);

when A represents S, then D represents a direct bond, C(O)N(H) or $CH_2C(O)NHNHC(S)NH$;

when A represents $N(R^{13})$, then D represents a direct bond, N(H), $S(O)_2$, C(O), C(O)CH(*c*-pentyl), C(O)N(H), C(S)N(H), $C(S)N(H)N{=}C(CH_3)$ or $N{=}C(R^{14b})$-;

when A represents C(O), then D represents a direct bond, $N(H)N{=}C(H)$-, N(H)N(H)C(O) or $N(R^{16})C(R^{17}){=}N$-;

when A represents $C(R^{13a}){=}$, then D represents N-N(H)C(O)N(H)-N=C(H);

R^{13} represents H, C_{1-4} alkyl, optionally substituted phenyl or Het^9;

R^{13a} represents H or C_{1-2} alkyl;

R^{14b} represents H or C_{1-4} alkyl;

R^{16} represents C_{1-4} alkyl or R^{16}, together with R^{17} and the N- and C-atoms to which those groups are attached, form a five-membered heterocyclic group containing at least one nitrogen atom (the atom to which R^{16} is attached) and optionally containing one further heteroatom selected from O and S, which heterocyclic group is optionally substituted by one or more groups selected from C_{1-4} alkyl, $=C(R^{18})R^{19}$ and *spiro*-$(CH_2)_p$;

R^{17} represents OR^{20d} or SR^{20e} or R^{17}, together with R^{16} and the N- and C-atoms to which those groups are attached, form a five-membered heterocyclic group containing at least one nitrogen atom (the atom to which R^{16} is attached) and optionally containing one further heteroatom selected from O and S, which heterocyclic group is optionally substituted by one or more groups selected from C_{1-4} alkyl, $=C(R^{18})R^{19}$ and *spiro*-$(CH_2)_p$;

R^{18} and R^{19} independently represent H or C_{1-2} alkyl;

p represents 4 or 5;

R^{20d} and R^{20e} independently represent C_{1-4} alkyl or optionally substituted phenyl;

Het^2 represents a four- to seven-membered monocyclic heterocyclic group or a nine- to eleven-membered bicyclic heterocyclic group, which heterocyclic group contains one to four heteroatoms selected from O, N and S, and which heterocyclic group is optionally substituted by one or more substituents selected from =O, cyano, halo, phenyl (which latter group is optionally substituted), C_{1-6} alkyl, $-N(R^{21c})R^{21d}$, $-C(O)R^{21e}$ and $C(O)OR^{21f}$;

Het^3 and Het^8 independently represent four to seven-membered heterocyclic groups containing one to four heteroatoms selected from O, N and S, which heterocyclic groups are optionally substituted by one or more substituents selected from cyano, halo, nitro, C_{1-6} alkyl, optionally substituted phenyl and $C(O)OR^{21f}$;

Het^5, Het^6 and Het^9 independently represent six- to ten-membered heterocyclic groups containing one to four heteroatoms selected from O, N

and S, which heterocyclic groups are optionally substituted by one or more substituents selected from =O, cyano, halo, C_{1-6} alkyl and optionally substituted phenyl;

optional substituents on phenyl groups are one or more substituents selected from $-OR^{21a}$, SR^{21b}, cyano, halo, nitro, C_{1-6} alkyl and $-NH_2$;

R^{21a} to R^{21f} independently represent H or C_{1-4} alkyl.

Preferred compounds of formula I also include those in which:

Het^1 represents a wholly aromatic fourteen-membered heterocyclic group containing one to three heteroatoms selected from O, N and S;

R^1 and R^2 independently represent one or more substituents on Ar^1 and Ar^2, respectively, which substituents are selected from halo, nitro, cyano, OR^3, SR^4, $N(R^5)R^6$, optionally substituted phenyl, Het^2, $C(O)R^7$, $C(R^{7a})=N-OR^{7b}$, $C(R^{7a})=N-N(H)R^{7b}$, $C(O)OR^8$, $C(O)N(R^9)R^{10}$, $S(O)_2$(optionally substituted phenyl) and C_{1-8} alkyl (which latter group is optionally unsaturated and/or substituted and/or terminated by one or more substituents selected from halo, cyano, $N(R^{5a})R^{6a}$ and optionally substituted phenyl);

R^5 represents $N=C(R^{5b})(R^{6b})$;

R^{5b} and R^{6b}, together with the C-atom to which they are attached, form a fully saturated, 5- or 6-membered monocyclic, or a partly aromatic 9- or 10-membered bicyclic, heterocyclic or carbocyclic ring system, wherein, when the ring system is heterocyclic, it contains a heteroatom selected from O, N and S, and wherein the carbocyclic or heterocyclic ring system is optionally substituted by one to three substituents selected from halo and =O;

R^{7a} represents C_{1-3} alkyl;

R^{7b} represents optionally substituted phenyl, $C(O)R^{7c}$ or $C(O)N(R^{7e})R^{7f}$;

R^{7c} represents C_{1-3} alkyl (optionally substituted by adamantyl) or Het^5;

R^{7e} represents H or C_{1-2} alkyl;

R^{7f} represents optionally substituted phenyl;

X represents the structural fragment

when A represents S, then D represents $CH_2C(O)$;

when A represents C(O), then D represents $N(R^{15j})C(O)N(R^{15k})$;

when A represents $C(R^{13a})=$, then D represents N-O, N-OC(O) or N-$OC(O)N(R^{13g})$;

R^{13g} represents H;

R^{15j} and R^{15k} represent H.

More preferred compounds of formula I include those in which:

Het^1 represents a wholly aromatic five- or six-membered monocyclic heterocyclic group containing one N-, O- or S-atom and optionally containing one or more further N-atoms, or Het^1 represents a nine- to eleven-membered wholly aromatic or part-aromatic heterocyclic group containing one or two heteroatoms selected from O, N and S;

R^1 and R^2 independently represent one or more optional substituents on Ar^1 and Ar^2, respectively, which substituents are selected from halo, nitro, cyano, OR^3, SR^4, $N(R^5)(R^6)$, phenyl (which latter group is optionally substituted by one or more substituents selected from halo, nitro and C_{1-4} alkyl), Het^2, $C(O)R^7$, $C(O)OR^8$, $C(O)N(R^9)(R^{10})$, $S(O)_2$(phenyl) (the phenyl part of which latter group is optionally substituted by one to three halo atoms) and C_{1-8} alkyl (which latter group is optionally unsaturated and/or substituted and/or terminated by (i) one or more substituents selected from halo, cyano and phenyl (which latter group is optionally substituted by one or more substituents selected from C_{1-4} alkyl and halo), or (ii) by cyano and $N(CH_3)_2$);

R^3 represents H, C_{1-4} alkyl (optionally substituted and/or terminated by (i) one or more halo atoms, or (ii) by phenyl), phenyl (which latter group is optionally substituted by one or more substituents selected from cyano,

halo, nitro and C_{1-6} alkyl), Het^3, $C(O)R^{12a}$ or $S(O)_2$(phenyl) (the phenyl part of which latter group is optionally substituted by one to three halo atoms);

R^4 represents C_{1-4} alkyl (optionally substituted and/or terminated by (i) one or more halo atoms, or (ii) by phenyl, which latter group is optionally substituted by one or more halo atoms) or phenyl (which latter group is optionally substituted by one or more substituents selected from cyano, halo, nitro and C_{1-6} alkyl);

R^5 and R^6 both represent H or R^5 represents H and R^6 represents phenyl (which latter group is optionally substituted by one or more halo atoms), $C(O)R^{12b}$ or $S(O)_2$(phenyl) (the phenyl part of which latter group is optionally substituted by one or more substituents selected from C_{1-4} alkyl and halo);

R^7 represents C_{1-2} alkyl or phenyl, which latter group is optionally substituted by one or more halo atoms;

R^8 represents H, C_{1-2} alkyl, Het^5 or phenyl, which latter group is optionally substituted by one or more substituents selected from halo, nitro and C_{1-4} alkyl;

R^9 represents Het^6 or $N(H)C(O)R^{12e}$;

R^{10} represents H or phenyl, which latter group is optionally substituted by one or more halo atoms;

R^{12a} and R^{12b} independently represent phenyl (optionally substituted by one or more substituents selected from OH, halo, nitro and C_{1-4} alkyl) or Het^8;

R^{12e} represents phenyl (optionally substituted by one or more substituents selected from cyano, halo, nitro and C_{1-6} alkyl);

n represents 3;

when A represents O, then D represents a direct bond, $S(O)_2$ or C(O);

when A represents $N(R^{13})$, then D represents N(H), $S(O)_2$, C(O), C(O)CH(*c*-pentyl), C(O)N(H), $C(S)N(H)N{=}C(CH_3)$ or $N{=}C(R^{14b})$-;

R^{13} represents H, C_{1-4} alkyl, phenyl (which latter group is optionally substituted by one or more substituents selected from cyano, halo, nitro and C_{1-6} alkyl) or Het^9;

R^{13a} represents H;

R^{14b} represents H or C_{1-2} alkyl;

R^{16}, together with R^{17} and the N- and C-atoms to which those groups are attached, form a five-membered heterocyclic group containing one nitrogen atom (the atom to which R^{16} is attached) and one S-atom, which heterocyclic group is optionally substituted by one to three groups selected from $=CH_2$ and *spiro*-$(CH_2)_5$;

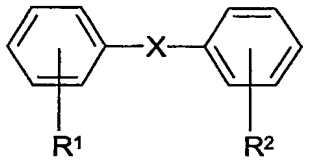
R^{17}, together with R^{16} and the N- and C-atoms to which those groups are attached, form a five-membered heterocyclic group containing one nitrogen atom (the atom to which R^{16} is attached) and one S-atom, which heterocyclic group is optionally substituted by one to three groups selected from $=CH_2$ and *spiro*-$(CH_2)_5$;

Het^2 represents a five- or six-membered wholly aromatic or fully saturated heterocyclic group containing one to three heteroatoms selected from O, N and S, which heterocyclic group is optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl and $C(O)O(C_{1-4}$ alkyl) or Het^2 represents a wholly or partly aromatic nine- or ten-membered bicyclic heterocyclic group containing one to three heteroatoms selected from O, N and S, which heterocyclic group is optionally substituted by one or more substituents selected from =O, halo, phenyl (which latter group is optionally substituted by one or more halo atoms) and C_{1-4} alkyl;

Het^3 and Het^8 independently represent five or six-membered heterocyclic groups containing one heteroatom selected from O, N and S and optionally containing one or two further N-atoms, which heterocyclic group is optionally substituted by one to three substituents selected from nitro, C_{1-3} alkyl, phenyl (which latter group is optionally substituted by one to three halo atoms) and $C(O)O(C_{1-4}$ alkyl);

Het^5, Het^6 and Het^9 independently represent nine- or ten-membered bicyclic aromatic heterocyclic groups containing one or two heteroatoms selected from O, N and S, which heterocyclic groups are optionally substituted by one or more substituents selected from =O, halo, C_{1-4} alkyl and phenyl.

Compounds of formula I that may be mentioned include compounds of formula Ia,



Ia

wherein R^1, R^2 and X are as hereinbefore defined.

Preferred compounds of formula Ia include those in which:

R^1 and R^2 independently represent one or more optional substituents selected from halo, nitro, C_{1-8} alkyl (which latter group is optionally unsaturated and/or substituted and/or terminated by (i) one or more halo atoms, or (ii) by cyano and phenyl (which latter group is optionally substituted by C_{1-2} alkyl)), OR^3, $N(H)R^6$, phenyl (which latter group is optionally substituted by one or more halo atoms) Het^2, $C(O)R^7$, $C(O)OR^8$, $S(O)_2$(phenyl) (the phenyl part of which latter group is optionally substituted by one or two halo atoms) and $C(O)N(H)N(H)C(O)R^{12e}$;

R^3 represents H, C_{1-4} alkyl (optionally substituted by phenyl), phenyl (which latter group is optionally substituted by one or more substituents selected from halo, nitro and C_{1-4} alkyl), Het^3, $C(O)R^{12a}$ or $S(O)_2$(phenyl) (the phenyl part of which latter group is optionally substituted by one or two halo atoms);

R^6 represents H or $S(O)_2$(phenyl) (the phenyl part of which latter group is optionally substituted by one or two C_{1-2} alkyl groups);

R^7 represents phenyl optionally substituted by one to three halo atoms;

R^8 represents H or phenyl (which latter group is optionally substituted by one to three substituents selected from halo, nitro and C_{1-2} alkyl);

R^{12a} represents phenyl (optionally substituted by one to three substituents selected from halo, nitro and C_{1-2} alkyl) or Het^8;

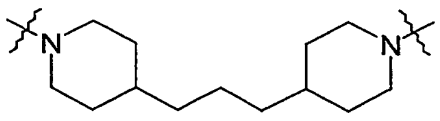
R^{12e} represents phenyl (optionally substituted by one or more substituents selected from halo and C_{1-4} alkyl);

Het^2 represents a five-membered aromatic heterocyclic group containing one or two heteroatoms selected from O, N and S, which heterocyclic group is optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl and $C(O)O(C_{1-2}$ alkyl) or Het^2 represents a partly aromatic ten-membered bicyclic heterocyclic group containing one or two heteroatoms selected from N and O, which heterocyclic group is optionally substituted by one or more substituents selected from =O and C_{1-2} alkyl;

Het^3 represents an aromatic five- or six-membered heterocyclic group containing one heteroatom selected from N and S and optionally containing one or two further N-atoms, which heterocyclic group is optionally substituted by nitro or $C(O)O(C_{1-2}$ alkyl);

Het^8 represents an aromatic five-membered heterocyclic group containing one heteroatom selected from N, O and S and optionally containing one or two further N-atoms, which heterocyclic group is optionally substituted by one to three substituents selected from C_{1-2} alkyl and phenyl (which latter group is optionally substituted by one or two halo atoms);

X represents a direct bond, O, S, $S(O)_2$, $SCH_2C(O)NHNHC(S)NH$, $OS(O)_2$, N(H)N(H), $N(H)S(O)_2$, $N(H)N=C(R^{14b})$-, $N(R^{13})C(O)$, N(H)C(O)CH(*c*-pentyl), N(H)C(S)N(H), $N(H)C(S)N(H)N=C(CH_3)$-, C(O)N(H)N=CH-, C(O)N(H)N(H)C(O), -CH=NN(H)C(O)N(H)N=CH- or the structural fragment



;

R^{13} represents H, phenyl (which latter group is optionally substituted by one or more substituents selected from halo and C_{1-4} alkyl) or Het^9;

R^{14b} represents H or ethyl;

Het^9 represents a nine-membered bicyclic aromatic heterocyclic group containing one or two heteroatoms selected from O, N and S, which heterocyclic group is optionally substituted by one or more halo or C_{1-4} alkyl groups.

More preferred compounds of formula Ia include those in which:

R^1 and R^2 independently represent one or more optional substituents selected from halo, nitro, C_{1-6} alkyl (which latter group is optionally unsaturated and/or substituted and/or terminated by (i) one or more halo atoms, or (ii) by cyano and phenyl (which latter group is optionally substituted by C_{1-2} alkyl))(e.g. methyl, trifluoromethyl, ethyl, *n*-propyl, *tert*-butyl, *n*-pentyl, *n*-hexyl, cyclohexyl or 2-(4-trifluoromethylphenyl)-1-cyanoethen-1-yl), OR^3, $N(H)R^6$, phenyl (which latter group is optionally substituted by one halo (e.g. fluoro) atom), Het^2, C(O)-phenyl, $C(O)OR^8$, $S(O)_2$(phenyl) (the phenyl part of which latter group is substituted by one or two chloro atoms) and $C(O)N(H)N(H)C(O)R^{12e}$;

R^3 represents H, C_{1-3} alkyl (e.g. methyl), benzyl, phenyl (which latter group is substituted by one to three substituents selected from C_{1-2} alkyl (which latter group is optionally substituted by one or more halo (e.g. fluoro) atoms) halo (e.g. chloro) and nitro), Het^3, $C(O)R^{12a}$ or $S(O)_2$(phenyl) (the phenyl part of which latter group is substituted by one or two chloro atoms);

R^6 represents H or $S(O)_2$(phenyl) (the phenyl part of which latter group is optionally substituted by one or two trifluoromethyl groups);

R^8 represents H or phenyl (which latter group is substituted by one to three substituents selected from bromo, nitro and C_{1-2} alkyl (which latter group is optionally substituted by one or more halo (e.g. fluoro) atoms));

R^{12a} represents phenyl (optionally substituted by one to three substituents selected from chloro, bromo, nitro and C_{1-2} alkyl (which latter group is optionally substituted by one or more halo (e.g. fluoro) atoms)) or Het^8;

R^{12e} represents phenyl substituted by C_{1-4} alkyl (e.g. *tert*-butyl);

R^{13} represents H or Het^9;

Het^9 represents a nine-membered bicyclic aromatic heterocyclic group containing two heteroatoms selected from N and S (e.g. benzothiazolyl).

When X represents a direct bond, preferred compounds of formula Ia include those in which:

R^1 and R^2 independently represent one or more optional substituents selected from C_{1-6} alkyl optionally substituted and/or terminated by one or more halo atoms (e.g. methyl, ethyl, *n*-propyl, *tert*-butyl, *n*-pentyl or *n*-hexyl), halo, nitro, NH_2, phenyl (which latter group is optionally substituted by fluoro) $C(O)OR^8$, $S(O)_2$(dichlorophenyl) and OR^3;

R^3 represents H, methyl, phenyl (which latter group is substituted by one or two substituents selected from halo (e.g. chloro), trifluoromethyl and nitro), pyridinyl (which latter group is substituted by nitro), $C(O)R^{12a}$ or $S(O)_2$(dichlorophenyl);

R^8 represents H or phenyl (which latter group is substituted by one to three substituents selected from bromo, nitro and trifluoromethyl);

R^{12a} represents phenyl (which latter group is substituted by one to three substituents selected from chloro, bromo, nitro and trifluoromethyl) or isoxazolyl (which latter group is substituted by one or two substituents selected from methyl and dichlorophenyl).

When X represents O, preferred compounds of formula Ia include those in which:

R^1 and R^2 independently represent one or more optional substituents selected from C_{1-6} alkyl (which latter group is (i) optionally substituted

and/or terminated by one or more halo atoms, or (ii) unsaturated and substituted by cyano and trifluoromethylphenyl) (e.g. methyl, trifluoromethyl, ethyl, *tert*-butyl, cyclohexyl or 2-(4-trifluoromethylphenyl)-1-cyanoethen-1-yl), chloro, bromo, nitro, benzoxazinonyl (which latter group is optionally substituted by methyl) (e.g. 5-methyl-4-oxo-4H-3,1-benzoxazin-2-yl) and OR^3;

R^3 represents phenyl (substituted by one or two substituents selected from nitro and trifluoromethyl) or benzyl.

When X represents S, preferred compounds of formula Ia include those in which:

R^1 and R^2 independently represent one or more optional substituents selected from C_{1-3} alkyl (e.g. methyl), chloro, nitro and OH.

When X represents $S(O)_2$, preferred compounds of formula Ia include those in which:

R^1 and R^2 independently represent one or more optional OR^3 groups;

R^3 represents phenyl (substituted by one or two substituents selected from nitro and trifluoromethyl).

When X represents $SCH_2C(O)NHNHC(S)NH$, preferred compounds of formula Ia include those in which:

R^1 and R^2 independently represent one or more optional substituents selected from chloro, nitro, C_{1-3} alkoxy (e.g. methoxy) and C_{1-3} alkyl, which latter group is optionally substituted and/or terminated by one or more halo (e.g. fluoro) atoms (e.g. trifluoromethyl).

When X represents $OS(O)_2$, preferred compounds of formula Ia include those in which:

R^1 and R^2 independently represent one or more optional substituents selected from C_{1-4} alkyl (e.g. *tert*-butyl), chloro, bromo and OR^3;

R^3 represents phenyl (substituted by one or two substituents selected from chloro and nitro).

When X represents N(H)N(H) or N(H)C(O)CH(*c*-pentyl), preferred compounds of formula Ia include those in which:

R^1 and R^2 independently represent one or more C_{1-4} alkyl substituents, which substituents are optionally substituted and/or terminated by one or more halo (e.g. fluoro) groups (e.g. trifluoromethyl).

When X represents $N(H)S(O)_2$, preferred compounds of formula Ia include those in which:

R^1 and R^2 independently represent one or more optional substituents selected from fluoro, chloro, nitro, C_{1-3} alkyl optionally substituted and/or terminated by one or more halo atoms (e.g. trifluoromethyl), OR^3, $NHS(O)_2$(di[trifluoromethyl]phenyl), pyrrolyl (e.g. 1-pyrrolyl), benzoxazinonyl (e.g. 4-oxo-4H-3,1-benzoxazin-2-yl) and pyrazolyl (which latter group is optionally substituted by one or two substituents selected from ethoxycarbonyl and trifluoromethyl) (e.g. 4-ethoxycarbonyl-5-trifluoromethyl-1H-pyrazol-1-yl);

R^3 represents methyl, phenyl (which latter group is substituted by one to three substituents selected from chloro, methyl and trifluoromethyl) or thienyl (which latter group is optionally substituted by ethoxycarbonyl) (e.g. 2-ethoxycarbonyl-3-thienyl).

When X represents N(H)N=CH- or N(H)N=C(Et)-, preferred compounds of formula Ia include those in which:

R^1 and R^2 independently represent one or more optional substituents selected from nitro, fluorophenyl and OR^3;

R^3 represents C_{1-3} alkyl (e.g. methyl) or C(O)-phenyl;

When X represents C(O)N(H)N=CH-, preferred compounds of formula Ia include those in which:

R^1 and R^2 independently represent one or more optional substituents selected from C_{1-4} alkyl (e.g. *tert*-butyl), chloro and OH.

When X represents $N(R^{13})C(O)$, preferred compounds of formula Ia include those in which:

R^1 and R^2 independently represent one or more optional substituents selected from C_{1-3} alkyl (which latter group is optionally substituted and/or terminated by one or more halo atoms) (e.g. trifluoromethyl), methoxy and fluorophenyl.

When X represents N(H)C(S)N(H), preferred compounds of formula Ia include those in which:

R^1 and R^2 independently represent one or more optional substituents selected from C_{1-4} alkyl (e.g. methyl), halo (e.g. chloro) and C(O)-phenyl.

When X represents $N(H)C(S)N(H)N=C(CH_3)$-, preferred compounds of formula Ia include those in which:

R^1 and R^2 independently represent one or more optional substituents selected from C_{1-4} alkyl (e.g. methyl), halo (e.g. chloro and/or bromo) and OH.

When X represents C(O)N(H)N(H)C(O), preferred compounds of formula Ia include those in which:

R^1 and R^2 independently represent one or more optional substituents selected from chloro, nitro, C_{1-4} alkyl (which latter group is optionally

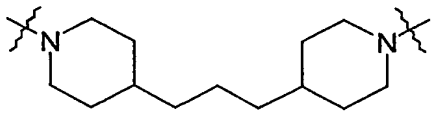
substituted and/or terminated by one or more halo atoms) (e.g. trifluoromethyl or *tert*-butyl) and $C(O)N(H)N(H)C(O)R^{12e}$;

R^{12e} represents *tert*-butylphenyl (e.g. 4-*tert*-butylphenyl).

When X represents -CH=NN(H)C(O)N(H)N=CH-, preferred compounds of formula Ia include those in which:

R^1 and R^2 independently represent one or more optional substituents selected from halo (e.g. chloro) and OH.

When X represents the structural fragment



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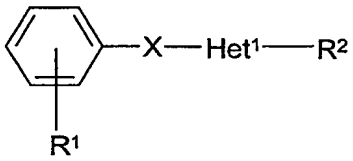
preferred compounds of formula Ia include those in which:

R^1 and R^2 independently represent one or more substituents selected from nitro and C_{1-4} alkyl, which latter group is optionally substituted and/or terminated by one or more halo (e.g. fluoro) groups (e.g. trifluoromethyl).

Compounds of formula I that may be mentioned also include compounds of formula Ib,



Ib

wherein Het^1, R^1, R^2 and X are as hereinbefore defined in respect of compounds of formula I.

Preferred compounds of formula Ib include those in which:

Het^1 represents a wholly aromatic five- or six-membered monocyclic heterocyclic group containing one N-, O- or S-atom and optionally containing one or more further N-atoms or Het^1 represents a nine- to eleven-

membered wholly aromatic or part-aromatic bicyclic heterocyclic group containing one or two heteroatoms selected from O, N and S;

R^1 and R^2 represent one or more optional substituents on the phenyl group and Het^1, respectively, which substituents are selected from halo, nitro, cyano, OR^3, SR^4, $N(R^5)(R^6)$, phenyl (which latter group is optionally substituted by one or more substituents selected from halo and C_{1-2} alkyl), Het^2, $C(O)R^7$, $C(O)OHet^5$, $C(O)N(R^9)(R^{10})$, $S(O)_2$(phenyl) (the phenyl part of which latter group is optionally substituted by one or two chloro atoms) and C_{1-8} alkyl (which latter group is (i) optionally substituted and/or terminated by cyano or one or more halo atoms, (ii) unsaturated and substituted and/or terminated by cyano and $N(CH_3)_2$, or (iii) interrupted by S and substituted or terminated by phenyl (which latter group is optionally substituted by one or more halo atoms));

R^3 represents H, C_{1-4} alkyl (which latter group is optionally substituted by one or more halo atoms) or phenyl (which latter group is optionally substituted by one to three substituents selected from halo, nitro and C_{1-2} alkyl);

R^4 represents C_{1-4} alkyl (optionally substituted and/or terminated by one or more fluoro atoms or by phenyl, which latter group is optionally substituted by one to three halo atoms) or phenyl (which latter group is optionally substituted by one or more substituents selected from halo and C_{1-4} alkyl);

R^5 and R^6 both represent H or R^5 represents H and R^6 represents phenyl (which latter group is optionally substituted by one to three halo atoms) or $C(O)R^{12b}$;

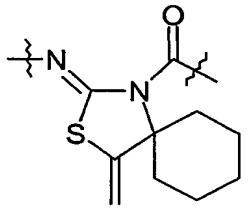
R^7 represents C_{1-2} alkyl;

R^9 represents Het^6;

R^{10} represents H or phenyl, which latter group is optionally substituted by one to three halo atoms;

R^{12b} represents phenyl (optionally substituted by one or two substituents selected from OH and halo) or Het^8;

X represents a direct bond, S, C(O), N(H), N(H)C(O), OC(O) (wherein, in which latter two groups, the C(O) group is attached either to Het^1 or to the phenyl group that bears R^1), N(H)C(O)N(H) or the structural fragment



wherein the wavy lines represent the points of attachment to the rest of the molecule and wherein the C(O) group is attached to Het^1;

Het^2 represents a wholly aromatic five-membered heterocyclic group containing one to three heteroatoms selected from O, N and S, which heterocyclic group is optionally substituted by methyl, Het^2 represents a fully saturated six-membered heterocyclic group containing one or two N-atoms, which heterocyclic group is optionally substituted by trifluoromethyl, or Het^2 represents a wholly or partly aromatic nine- or ten-membered heterocyclic group containing one or two heteroatoms selected from N and O, which heterocyclic group is optionally substituted by one to three substituents selected from =O, halo and phenyl (which latter group is optionally substituted by halo);

Het^5 represents a nine- or ten-membered heterocyclic group containing one or two heteroatoms selected from N and O, which heterocyclic group is optionally substituted by one to three substituents selected from =O, halo and phenyl;

Het^6 represents a nine-membered bicyclic aromatic heterocyclic group containing one or two heteroatoms selected from O, N and S;

Het^8 represents a five-membered heterocyclic group containing one heteroatom selected from O, N and S, which heterocyclic group is optionally substituted by one or two substituents selected from methyl and

phenyl (which latter group is optionally substituted by one or two halo atoms).

More preferred compounds of formula Ib include those in which Het^1 represents:

benzimidazolyl (e.g. 5-{2-[4-chlorophenyl]-1H-benzimidazol-5-yl}-1H-benzimidazol-2-yl);

benzofuranyl (e.g. 5,7-dichlorobenzofuran-2-yl or 5-nitrobenzofuran-2-yl);

benzothiazolyl (e.g. benzothiazol-2-yl);

benzothiophenyl (e.g. benzothiophen-2-yl or 3-chlorobenzothiophen-2-yl);

1,5-dihydrobenzo[e][1,3]dithiepinyl (e.g. 3,7,8-trimethyl-1,5-dihydro-benzo[e][1,3]dithiepine);

furanyl (e.g. 2-acetylfuran-5-yl);

indolyl (e.g. 5-methoxy-3-methylindol-2-yl);

isoxazolyl (e.g. 3-(2-chlorophenyl)isoxazol-4-yl, 3-(2,6-dichlorophenyl)-5-methylisoxazol-4-yl, 3-(2-chloro-6-fluorophenyl)-5-methylisoxazol-4-yl, 3-(7-chloro-2-benzoxazin-4-onyl)-5-methylisoxazol-4-yl or 4-[*N*-(benzothiazol-2-yl)-*N*-(3-chlorophenyl)aminocarbonyl]-5-methylisoxazol-3-yl);

oxadiazolyl (e.g. 5-(3-chromen-2-onyl)-1,2,4-oxadiazol-3-yl or 5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl);

oxazolyl (e.g. 4,5-diphenyloxazol-2-yl);

pyrazolyl (e.g. 3-(2-furanyl)-5-{[2-methyl-5-(4-chlorophenyl)-3-furanyl]-carbonylamino}-1H-pyrazol-1-yl);

pyridinyl (e.g. 2-(4-trifluoromethylpiperidin-1-yl)pyridin-3-yl, 2-(4-trifluoromethylpiperidin-1-yl)pyridin-5-yl, 2-[(4-chlorophenyl)thio]pyridin-5-yl, 2,6-bis(phenylthio)pyridin-3-yl or 2-phenyl-4-(2-thienyl)pyridin-6-yl);

pyrrolyl (e.g. 1-pyrrolyl);

quinolinyl (e.g. 2-amino-6-chloro-3-cyanoquinolin-4-yl);

tetrazolyl (e.g. 1,2,3,4-tetrazol-5-yl);

thiadiazolyl (e.g. 5-trifluoromethyl-1,3,4-thiadiazol-2-yl); and

thiazolyl (e.g. 5-methyl-2-(2-thienyl)thiazol-4-yl, 5-methyl-2-(5-methyl-1,2,3-thiadiazol-4-yl)thiazol-4-yl, 2-(4-chlorophenyl)-5-methylthiazol-4-yl, 5-methyl-2-(phenylamino)thiazol-4-yl, 2-(3,5-dichlorophenylamino)-5-methylthiazol-4-yl, 2-(5-chloro-2-hydroxyphenylcarbonylamino)thiazol-4-yl, 2-(1-cyano-2-dimethylaminoethen-1-yl)thiazol-4-yl or 5-nitrothiazol-2-yl).

More preferred compounds of formula Ib also include those in which:

R^1 and R^2 represent one or more optional substituents on the phenyl group and Het^1, respectively, which substituents are selected from halo, nitro, cyano, OR^3, SR^4, $N(H)(R^6)$, phenyl (which latter group is optionally substituted by one or two of fluoro, chloro and ethyl), Het^2, $C(O)CH_3$, $C(O)OHet^5$, $C(O)N(R^9)(R^{10})$, $S(O)_2$(chlorophenyl) and C_{1-6} alkyl (which latter group is (i) optionally substituted and/or terminated by one or more halo atoms , (ii) substituted by cyano, (iii) unsaturated and substituted and/or terminated by cyano and $N(CH_3)_2$, or (iv) interrupted by S and terminated by dihalophenyl) (e.g. methyl, trifluoromethyl, *tert*-butyl, cyclohexyl, cyanomethyl, 1-cyano-2-dimethylamino-ethen-1-yl or 2-(2-chloro-6-fluorobenzylthio)ethyl);

R^3 represents phenyl (optionally substituted by one to three substituents selected from nitro and trifluoromethyl) or C_{1-2} alkyl optionally substituted and/or terminated by one or more halo (e.g. fluoro) atoms;

R^4 represents C_{1-2} alkyl (which latter group is optionally substituted and/or terminated by one or more fluoro atoms), phenyl (which latter group is optionally substituted by one or more halo (e.g. chloro) atoms) or benzyl (the phenyl part of which is optionally substituted by one or two halo (e.g. chloro) atoms);

R^6 represents phenyl (which latter group is optionally substituted by one or two halo (e.g. chloro) atoms) or $C(O)R^{12b}$;

R^9 represents Het^6;

R^{10} represents phenyl, which latter group is optionally substituted by one or two halo (e.g. chloro) atoms;

R^{12b} represents Het^8 or phenyl (which latter group is substituted by one or two substituents selected from OH and chloro);

Het^5 represent dihydroquinazoline optionally substituted by =O and/or phenyl (e.g. 4-oxo-2-phenyl-3,4-dihydroquinazolin-3-yl);

Het^6 represents benzothiazolyl (e.g. benzothiazol-2-yl);

Het^8 represents furanyl (e.g. 2-(4-chlorophenyl)-5-methyl-4-furanyl).

When X represents a direct bond, preferred compounds of formula Ib include those in which:

Het^1 represents benzimidazolyl, 1,5-dihydrobenzo[e][1,3]dithiepinyl, furanyl, indolyl, isoxazolyl, oxadiazolyl, pyrazolyl, pyridinyl, pyrrolyl, quinolinyl, tetrazolyl or thiazolyl ;

R^1 and R^2 independently represent one to three optional substituents selected from halo (e.g. chloro or fluoro), cyano, nitro, C_{1-6} alkyl (e.g. methyl, trifluoromethyl or cyclohexyl), methoxy, $C(O)CH_3$, NH_2, thienyl (e.g. 2-thienyl), furanyl, 4-methyl-1,2,3-thiadiazol-5-yl, 2-(4-chlorophenyl)-1H-benzimidazol-6-yl, 5-fluoro-4-oxo-3,1-benzoxazin-2-yl, 5-iodo-4-oxo-3,1-benzoxazin-2-yl, 6-chloro-4-oxo-3,1-benzoxazin-2-yl, 2-oxo-chromen-3-yl, phenyl, 2-fluorophenyl, 4-chlorophenyl, (4-chlorophenyl)methylthio, phenylamino, 3,5-dichlorophenylamino, *N*-(benzothiazol-2-yl)-*N*-(3-chlorophenyl)aminocarbonyl, 1-cyano-2-dimethylaminoethen-1-yl, (5-chloro-2-hydroxyphenyl)carbonylamino, [2-methyl-5-(4-chlorophenyl)-3-furanyl]carbonylamino and (4-oxo-2-phenyl-3,4-dihydroquinazolinyl)oxy-carbonyl.

When X represents C(O), preferred compounds of formula Ib include those in which:

Het^1 represents benzofuranyl;

R^1 and R^2 independently represent halo, nitro, phenyl or OR^3;

R^3 represents methyl optionally substituted by one or more halo (e.g. fluoro) atoms.

When X represents N(H)C(O)N(H), preferred compounds of formula Ib include those in which:

Het^1 represents pyridinyl;

R^1 and R^2 independently represent one to three optional substituents selected from fluoro, chloro, nitro, trifluoromethoxy, SR^4 and 4-(trifluoromethyl)piperidin-1-yl;

R^4 represents methyl optionally substituted by one or more fluoro atoms or R^4 represents phenyl (which latter group is optionally substituted by a halo (e.g. chloro) atom).

When X represents OC(O), preferred compounds of formula Ib include those in which:

Het^1 represents benzothiophenyl;

R^1 and R^2 independently represent halo (e.g. fluoro or chloro), nitro, C_{1-4} alkyl (which latter group is optionally substituted by cyano) (e.g. methyl, cyanomethyl or *tert*-butyl), dihalophenyl (e.g. 2-chloro-6-fluorophenyl or 2-chloro-4-fluorophenyl), $S(O)_2$(4-chlorophenyl) or OR^3;

R^3 represents phenyl substituted by nitro and trifluoromethyl.

When X represents S, preferred compounds of formula Ib include those in which:

Het^1 represents oxazolyl or thiazolyl;

R^1 and R^2 independently represent one to three optional substitutents selected from halo (e.g. chloro), nitro, NH_2, phenyl and 1-pyrrolyl.

When X represents N(H), preferred compounds of formula Ib include those in which:

Het^1 represents benzothiazolyl;

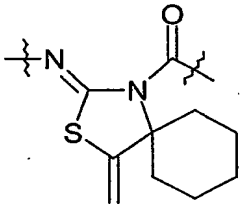
R^1 and R^2 independently represent one to three optional C_{1-2} alkyl substitutents, which substituents are substituted by one or more halo (e.g. fluoro) atoms (e.g. trifluoromethyl).

When X represents N(H)C(O), preferred compounds of formula Ib include those in which:

Het^1 represents benzothiophenyl, pyrrolyl or thiadiazolyl;

R^1 and R^2 independently represent one to three optional substitutents selected from halo (e.g. chloro), C_{1-3} alkyl (which latter group is (i) substituted by one or more halo (e.g. fluoro) atoms, or (ii) interrupted by S and terminated by fluorochlorophenyl) (e.g. trifluoromethyl or 2-(2-chloro-6-fluorobenzylthio)ethyl) phenyl, ethylphenyl (e.g.4-ethylphenyl) and 1-piperidinyl.

When X represents the structural fragment



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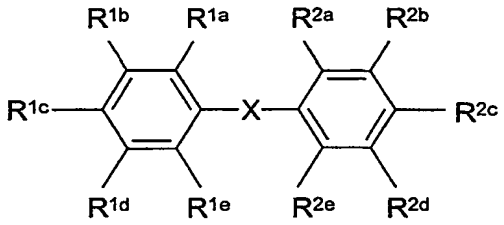
preferred compounds of formula Ib include those in which R^1 and R^2 independently represent halo (e.g. chloro).

Preferred compounds of formulae I, Ia and Ib also include those in which at least one of R^1 and R^2 represents at least one substituent as hereinbefore defined in respect of R^1 and R^2.

Compounds of formula I that may be mentioned also include compounds of formula Ic:



wherein X is as hereinbefore defined and R^{1a} to R^{1e} and R^{2a} to R^{2e} represent H or R^1 or R^2 as hereinbefore defined in respect of compounds of formulae I and Ia.

When X represents a direct bond, preferred compounds of formula Ic include those in which:

(a) R^{1a} is other than H and R^{1b}, R^{1c}, R^{1d} and R^{1e} all represent H;

(b) R^{1c} is other than H and R^{1a}, R^{1b}, R^{1d} and R^{1e} all represent H;

(c) R^{2c} is other than H and R^{2a}, R^{2b}, R^{2d} and R^{2e} all represent H;

(d) R^{1a} to R^{1e} all represent H;

(e) R^{1b}, R^{1c} and R^{1d} are all other than H and R^{1a} and R^{1e} both represent H;

(f) R^{2b}, R^{2c} and R^{2d} are all other than H and R^{2a} and R^{2e} both represent H;

(g) R^{1b} and R^{1c} are both other than H and R^{1a}, R^{1d} and R^{1e} all represent H;

(h) R^{2b} and R^{2c} are both other than H and R^{2a}, R^{2d} and R^{2e} all represent H;

When X represents a direct bond, more preferred compounds of formula Ic include those in which:

(a) R^{1a} and R^{2c} are both other than H and R^{1b}, R^{1c}, R^{1d}, R^{1e}, R^{2a}, R^{2b}, R^{2d} and R^{2e} all represent H;

(b) R^{1c} and R^{2c} are both other than H and R^{1a}, R^{1b}, R^{1d}, R^{1e}, R^{2a}, R^{2b}, R^{2d} and R^{2e} all represent H;

(c) R^{2c} is other than H and R^{1a} to R^{1e}, R^{2a}, R^{2b}, R^{2d} and R^{2e} all represent H;

(d) R^{1b}, R^{1c}, R^{2b} and R^{2c} are all other than H and R^{1a}, R^{1d}, R^{1e}, R^{2a}, R^{2d} and R^{2e} all represent H;

(e) R^{1b}, R^{1c}, R^{1d}, R^{2b}, R^{2c} and R^{2d} are all other than H and R^{1a}, R^{1e}, R^{2a} and R^{2e} all represent H.

When R^{1a} is other than H, it preferably represents halo (e.g. chloro or, particularly, fluoro) or nitro.

When R^{1b} is other than H, it preferably represents halo (e.g. chloro or bromo), nitro or C_{1-6} alkyl (e.g. C_{1-4} alkyl, such as *tert*-butyl).

When R^{1c} is other than H, it preferably represents:

halo (such as bromo or iodo),

nitro,

NH_2,

C_{1-6} alkyl (e.g. methyl, ethyl, *n*-propyl or *n*-pentyl),

OR^3 (wherein R^3 represents, for example,

H,

aryl, for example phenyl optionally substituted by one to three substituents selected from halo, nitro and C_{1-4} alkyl (e.g. phenyl substituted in the *para*- and/or *ortho*-positions by one to three substituents selected from trifluoromethyl, nitro and halo (e.g. chloro)),

Het^3, for example pyridinyl optionally substituted by nitro (e.g. pyridin-2-yl substituted in the 3- or the 5-position by nitro),

$C(O)R^{12a}$, wherein R^{12a} represents, for example, phenyl optionally substituted by one to three substituents selected from halo, nitro and C_{1-4} alkyl (e.g. phenyl substituted in the *para*- and/or *ortho*-positions by one to three substituents selected from trifluoromethyl, nitro and halo (e.g. chloro or bromo)) or R^{12a} represents Het^8, for example a 5-membered aromatic heterocyclic group containing 2 or 3 heteroatoms selected from N, O and S, which heterocyclic group is optionally

substituted by one to three substituents selected from phenyl (optionally substituted by one to three halo (e.g. chloro) groups) and C_{1-4} alkyl (e.g. methyl), or

SO_2-aryl, for example SO_2-phenyl, wherein the phenyl group is optionally substituted by one to three halo groups (e.g. two chloro groups)),

$C(O)OR^8$ (wherein R^8 represents, for example, phenyl optionally substituted by one to three substituents selected from halo, nitro and C_{1-4} alkyl (e.g. phenyl substituted in the *para*- and one or both of the *ortho*-positions by substituents selected from trifluoromethyl, nitro and halo (e.g. bromo))),

$C(O)N(H)R^{10}$, wherein R^{10} represents Het^8, for example a 5-membered aromatic heterocyclic group containing 2 or 3 heteroatoms selected from N, O and S, which heterocyclic group is optionally substituted by one or two C_{1-4} alkyl (e.g. trifluoromethyl) groups; or

$S(O)_2R^{11}$, wherein R^{11} represents aryl, for example phenyl optionally substituted by one to three substituents selected from halo (e.g. chloro) and $N(H)S(O)_2$-phenyl, which latter phenyl group is optionally substituted by one or two halo (e.g. chloro) groups.

When R^{1d} is other than H, it preferably represents halo (e.g. bromo) or C_{1-6} alkyl (e.g. C_{1-4} alkyl, such as *tert*-butyl).

When R^{1e} is other than H, it preferably represents halo (e.g. chloro) or nitro.

R^{2a} preferably represents H.

When R^{2b} is other than H, it preferably represents halo (e.g. chloro or bromo), nitro, aryl (e.g. unsubstituted phenyl) or C_{1-6} alkyl (e.g. C_{1-4} alkyl, such as *tert*-butyl).

When R^{2c} is other than H, it preferably represents:

halo (such as bromo or iodo),

nitro,

$N(H)R^5$ (wherein R^5 represents, for example H or $N=C(R^{5b})(R^{6b})$, wherein R^{5b} and R^{6b}, together with the C-atom to which they are attached, form a 10-membered bicyclic, partly aromatic, heterocyclic ring system, wherein the ring system contains one or two heteroatoms (located, for example, in the non-aromatic ring) selected from O, N and S, and wherein the heterocyclic ring system is optionally substituted by one to three substituents selected from halo (e.g. bromo) and =O),

C_{1-6} alkyl (e.g. methyl, ethyl, *n*-propyl, *n*-pentyl or *n*-hexyl),

Het^3, for example

a 9- or 10-membered bicyclic aromatic heterocycle containing one or two heteroatoms selected from N, O and S (e.g. indolyl), which heterocycle is optionally substituted by one to three substituents selected from C_{1-4} alkyl (e.g. methyl) and C_{1-4} alkoxy (e.g. methoxy), or

a 5-membered aromatic heterocycle containing one to three heteroatoms selected from N, O and S (e.g. thiazolyl, such as thiazol-4-yl), which heterocycle is optionally substituted by one or two substituents (located, for example, at the 2- and/or 5-positions of the ring) selected from C_{1-4} alkyl (e.g. methyl), aryl (such as phenyl optionally substituted by one or two halo (e.g. chloro) groups), $N(H)R^{21d}$ (wherein R^{21d} represents, for example, phenyl optionally substituted by one to three halo (e.g. chloro) groups) and $N(H)C(O)R^{21j}$ (wherein R^{21j} represents, for example, phenyl optionally substituted by one to three substituents selected from halo (e.g. chloro) and hydroxy),

OR^3 (wherein R^3 represents, for example,

H,

C_{1-4} alkyl (e.g. methyl),

aryl, for example phenyl optionally substituted by one to three substituents selected from halo, nitro and C_{1-4} alkyl (e.g. phenyl substituted in the *para*- and/or *ortho*-positions by one to three substituents selected from trifluoromethyl, nitro and halo (e.g. chloro)),

Het^3, for example pyridinyl optionally substituted by nitro (e.g. pyridin-2-yl substituted in the 3- or the 5-position by nitro),

$C(O)R^{12a}$, wherein R^{12a} represents, for example, phenyl optionally substituted by one to three substituents selected from halo, nitro and C_{1-4} alkyl (e.g. phenyl substituted in the *para*- and/or *ortho*-positions by one to three substituents selected from trifluoromethyl, nitro and halo (e.g. chloro or bromo)) or R^{12a} represents Het^8, for example a 5-membered aromatic heterocyclic group containing 2 or 3 heteroatoms selected from N, O and S, which heterocyclic group is optionally substituted by one to three substituents selected from phenyl (optionally substituted by one to three halo (e.g. chloro) groups) and C_{1-4} alkyl (e.g. methyl), or

SO_2-aryl, for example SO_2-phenyl, wherein the phenyl group is optionally substituted by one to three halo groups (e.g. two chloro groups)),

$C(R^{7a})$=N-OR^{7b} (wherein R^{7a} represents, for example, C_{1-4} alkyl (e.g. ethyl) and R^{7b} represents, for example

aryl, for example phenyl optionally substituted by one to three substituents selected from nitro and C_{1-4} alkyl (e.g. trifluoromethyl),

$C(O)R^{7c}$, wherein R^{7c} represents, for example, Het^5 (which may represent, for example, a 5-membered aromatic heterocycle containing one or two heteroatoms selected from N, O and S (e.g. thienyl)) or C_{1-6} alkyl optionally substituted by adamantyl (e.g. adamantylmethyl), or

$C(O)N(H)R^{7f}$, wherein R^{7f} represents, for example, aryl, such as phenyl optionally substituted by one to three halo (e.g. chloro) groups),

$C(R^{7a})=N-N(H)R^{7b}$ (wherein R^{7a} represents, for example, C_{1-4} alkyl (e.g. ethyl) and R^{7b} represents, for example, aryl, such as phenyl optionally substituted by one or two nitro groups),

$C(O)R^7$ (wherein R^7 represents, for example, Het^5, such as an aromatic 9- or 10-membered bicyclic heterocycle containing one to three heteroatoms selected from N, O and S (e.g. benzofuranyl)),

$C(O)OR^8$ (wherein R^8 represents, for example, H or phenyl optionally substituted by one to three substituents selected from halo, nitro and C_{1-4} alkyl (e.g. phenyl substituted in the *para*- and one or both of the *ortho*-positions by substituents selected from trifluoromethyl, nitro and halo (e.g. bromo))),

$C(O)N(H)R^{10}$, wherein R^{10} represents

aryl, for example phenyl optionally substituted by one or two substituents selected from C_{1-4} alkyl (e.g. trifluoromethyl) and C_{1-4} alkoxy (e.g. methoxy), or

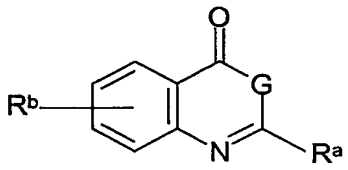
Het^8, for example a 5-membered aromatic heterocyclic group containing 2 or 3 heteroatoms selected from N, O and S, which heterocyclic group is optionally substituted by one or two C_{1-4} alkyl (e.g. trifluoromethyl) groups; or

$S(O)_2R^{11}$, wherein R^{11} represents aryl, for example phenyl optionally substituted by one to three substituents selected from halo (e.g. chloro) and $N(H)S(O)_2$-phenyl, which latter phenyl group is optionally substituted by one or two halo (e.g. chloro) groups.

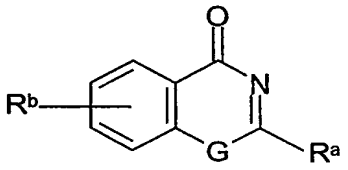
When R^{2d} is other than H, it preferably represents halo (e.g. bromo), aryl (e.g. unsubstituted phenyl) or C_{1-6} alkyl (e.g. C_{1-4} alkyl, such as *tert*-butyl).

R^{2e} preferably represents H.

According to a third aspect of the invention there is provided the use of a compound of formula IIa or IIb,



IIa



IIb

wherein

R^a represents aryl, Het^a or C_{1-12} alkyl, which latter group is optionally substituted and/or terminated by one or more substituents selected from halo, OR^c, aryl and Het^b, or R^a, together with R^d and the C- and N-atoms to which they are attached, form a 5- or 6-membered heterocyclic ring containing one N-atom (the atom to which R^d is attached) and optionally containing one or more further heteroatoms selected from N, O and S, which heterocyclic ring is fully saturated, partially unsaturated or aromatic in character and is optionally substituted by one or more substituents selected from =O, OH, halo, nitro, cyano, C_{1-6} alkyl, aryl, NH_2 and $C(O)R^{d1}$;

R^c represents H, C_{1-6} alkyl or aryl;

R^{d1} represents H, C_{1-6} alkyl or aryl;

R^b represents one or more optional substituents selected from halo, nitro, cyano, -SCN, C_{1-6} alkyl and NH_2;

G represents O or $N(R^d)$;

R^d represents H, C_{1-12} alkyl, aryl, Het^c or R^d, together with R^a and the N- and C-atoms to which they are attached, form a 5- or 6-membered heterocyclic ring containing one N-atom (the atom to which R^d is attached) and optionally containing one or more further heteroatoms selected from N,

O and S, which heterocyclic ring is fully saturated, partially unsaturated or aromatic in character and is optionally substituted by one or more substituents selected from =O, OH, halo, nitro, cyano, C_{1-6} alkyl, aryl, NH_2 and $C(O)R^{d1}$; and

Het^a, Het^b and Het^c independently represent four- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from N, O and S, which heterocyclic groups are optionally substituted by one or more substituents selected from =O, OH, halo, nitro, cyano, C_{1-6} alkyl, aryl and NH_2;

wherein each aryl group, unless otherwise specified, is optionally substituted;

or a pharmaceutically acceptable derivative thereof;

for the preparation of a medicament for the treatment of cancer.

The skilled person will appreciate that for compounds of formula IIa or IIb in which G represents NH, the structures drawn for IIa and IIb may in fact represent different tautomers of the same compound.

Het^a, Het^b and Het^c groups that may be mentioned include those containing 1 to 4 heteroatoms (selected from the group oxygen, nitrogen and/or sulfur) and in which the total number of atoms in the ring system are between five and twelve. Het^a, Het^b and Het^c groups may be fully saturated, partly unsaturated, wholly aromatic, partly aromatic and/or bicyclic in character. Heterocyclic groups that may be mentioned in relation to Het^a, Het^b and Het^c include benzodioxanyl, benzodioxepanyl, benzodioxolyl, benzofuranyl, benzofurazanyl, benzimidazolyl, benzomorpholinyl, benzothiazolyl, benzothiophenyl, chromanyl, chromenonyl, cinnolinyl,

dioxanyl, furanyl, hydantoinyl, imidazolyl, imidazo[1,2-*a*]pyridinyl, indolyl, isoquinolinyl, isoxazolyl, maleimido, morpholinyl, oxazolyl, phthalazinyl, phthalimido, piperazinyl, piperidinyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrrolidinonyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 3-sulfolenyl, tetrahydropyranyl, tetrahydrofuranyl, thiazolyl, thienyl, thiochromanyl, triazolyl and the like. Values of Het^a that may be mentioned include benzothiophenyl, chromenonyl, furanyl and thienyl. Values of Het^b that may be mentioned include furanyl. Values of Het^c that may be mentioned include phthalimido.

Substituents on Het (Het^a to Het^c) groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point of attachment of Het (Het^a to Het^c) groups may be *via* any atom in the ring system including (where appropriate) a heteroatom, or an atom on any fused carbocyclic ring that may be present as part of the ring system. Het (Het^a to Het^c) groups may also be in the *N*- or *S*-oxidised form.

Compounds of formulae IIa and IIb that may be mentioned include those in which:

R^a represents aryl, Het^a or C_{1-12} alkyl, which latter group is optionally substituted and/or terminated by one or more substituents selected from halo, OR^c, aryl and Het^b;

Het^a, Het^b and Het^c independently represent four- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from N, O and S, which heterocyclic groups are optionally substituted by one or more substituents selected from =O, OH, halo, nitro, cyano, C_{1-6} alkyl and NH_2.

Further compounds of formulae IIa and IIb that may be mentioned include those in which at least one of the following applies:

(i) R^a, together with R^d and the C- and N-atoms to which they are attached, form a 5- or 6-membered heterocyclic ring containing one N-atom (the atom to which R^d is attached) and optionally containing one or more further heteroatoms selected from N, O and S, which heterocyclic ring is fully saturated, partially unsaturated or aromatic in character and is optionally substituted by one or more substituents selected from =O, OH, halo, nitro, cyano, C_{1-6} alkyl, aryl, NH_2 and $C(O)R^{d1}$;

(ii) Het^a, Het^b and Het^c independently represent four- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from N, O and S, which heterocyclic groups are substituted by aryl and are optionally substituted by one or more further substituents selected from =O, OH, halo, nitro, cyano, C_{1-6} alkyl, aryl and NH_2.

Preferred compounds of formulae IIa and IIb include those in which:

R^a represents optionally substituted phenyl, Het^a or C_{1-6} alkyl, which latter group is optionally unsaturated and/or branched and/or substituted or terminated by (i) one or more halo groups or (ii) one group selected from OR^c, optionally substituted phenyl and Het^b;

R^c represents optionally substituted phenyl;

R^b represents one or more optional substituents selected from halo, nitro, -SCN and C_{1-4} alkyl;

R^d represents H, C_{1-4} alkyl, Het^c or optionally substituted phenyl;

Het^a and Het^c independently represent a wholly or partly aromatic five- to ten-membered heterocyclic group containing one or two heteroatoms selected from N, O and S, which heterocyclic group is optionally substituted by one to three substituents selected from =O, halo, nitro, cyano and C_{1-4} alkyl;

Het^b represents an aromatic five- or six-membered heterocyclic group containing one to three heteroatoms selected from N, O and S, which

heterocyclic group is optionally substituted by one to three substituents selected from halo, cyano and C_{1-4} alkyl;

optional substituents on phenyl groups are one or more substituents selected from halo (e.g. fluoro, chloro or bromo), cyano, nitro and C_{1-4} alkyl (which latter group is optionally branched and/or substituted by one or more halo atoms).

Preferred compounds of formulae IIa and IIb also include those in which R^a, together with R^d and the C- and N-atoms to which they are attached, form a 5-membered heterocyclic ring containing one N-atom (the atom to which R^d is attached) and one or two further heteroatoms selected from N, O and S, which heterocyclic ring is partially unsaturated and is optionally substituted by $C(O)R^{d1}$;

R^{d1} represents phenyl optionally substituted by one to three halo (e.g. chloro) groups;

Het^a and Het^c independently represent a wholly or partly aromatic five- to ten-membered heterocyclic group containing one or two heteroatoms selected from N, O and S, which heterocyclic group is substituted by phenyl and is optionally substituted by one or two further substituents selected from =O, halo, nitro, cyano and C_{1-4} alkyl;

optional substituents on phenyl groups are one or more substituents selected from halo (e.g. fluoro, chloro or bromo), cyano, nitro, C_{1-4} alkyl (which latter group is optionally branched and/or substituted by one or more halo atoms) and $N(H)S(O)_2$-phenyl, which latter phenyl group is optionally substituted by one or two halo (e.g. fluoro) groups.

More preferred compounds of formulae IIa and IIb include those in which:

R^a represents phenyl (optionally substituted by one or two substituents selected from chloro, fluoro, cyano, nitro, methyl, trifluoromethyl and *tert*-butyl), Het^a, methyl (which latter group is optionally substituted by OR^c) or

unsaturated and/or branched C_{2-4} alkyl (which latter group is optionally substituted or terminated by one group selected from phenyl and Het^b);

R^c represents phenyl optionally substituted by one or two halo (e.g. chloro) atoms;

R^b represents one to three optional substituents selected from fluoro, chloro, bromo, iodo, nitro, -SCN and methyl;

R^d represents H, methyl, Het^c or phenyl (which latter group is optionally substituted by one or two substituents selected from fluoro, chloro, methyl and trifluoromethyl);

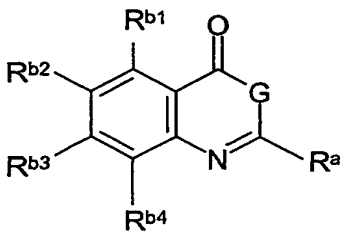
Het^a represents an aromatic five-membered heterocyclic group containing one or two heteroatoms selected from N, O and S, which heterocyclic group is optionally substituted by one or two substituents selected from halo (e.g. bromo) and nitro or Het^a and Het^c independently represent wholly or partly aromatic nine- or ten-membered heterocyclic groups containing one or two heteroatoms selected from N, O and S, which heterocyclic group is optionally substituted by one or two substituents selected from =O and halo (e.g. chloro);

Het^b represents furanyl (e.g. 2-furanyl) or thienyl.

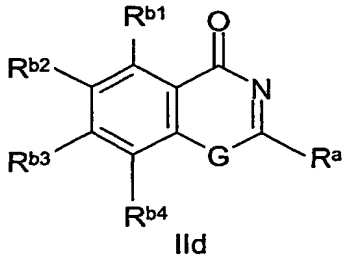
Preferred compounds of formula IIa include those in which R^d represents methyl, *N*-phthalimido, 4-fluorophenyl, 4-methylphenyl, 3-trifluoromethyl-phenyl or 3,4-dichlorophenyl.

Preferred compounds of formula IIb include those in which R^d represents H.

Preferred compounds of formulae IIa and IIb also include compounds of formulae IIc and IId, respectively,



IIc



IId

wherein R^a and G are as hereinbefore defined and R^{b1} to R^{b4} independently represent H or R^b as hereinbefore defined.

Preferred compounds of formulae IIc and IId include those in which:

(a) R^{b1} to R^{b4} all represent H;

(b) R^{b2} is other than H and R^{b1}, R^{b3} and R^{b4} all represent H;

(c) R^{b1} is other than H and R^{b2} to R^{b4} all represent H;

(d) R^{b3} is other than H and R^{b1}, R^{b2} and R^{b4} all represent H;

(e) R^{b2} and R^{b4} are both other than H and R^{b1} and R^{b3} both represent H;

(f) R^{b1}, R^{b2} and R^{b4} are all other than H and R^{b3} represents H.

Preferred compounds include those of formula IIc in which G represents O.

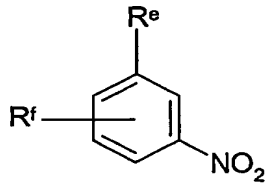
When R^{b1} is other than H, it preferably represents halo (e.g. fluoro or chloro) or C_{1-4} alkyl (e.g. methyl).

When R^{b2} is other than H, it preferably represents halo (e.g. chloro, bromo or iodo), nitro, -SCN or C_{1-4} alkyl (e.g. methyl).

When R^{b3} is other than H, it preferably represents halo (e.g. chloro).

When R^{b4} is other than H, it preferably represents halo (e.g. chloro or bromo) or C_{1-4} alkyl (e.g. methyl).

According to a fourth aspect of the invention, there is provided the use of a compound of formula III,



III

wherein R^e represents $C(O)OR^g$, $C(O)N(R^h)(R^i)$ or $S(O)_2N(R^h)(R^i)$;

R^f represents one or more optional substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy and halo;

R^g represents C_{1-6} alkyl; and

R^h and R^i independently represent, at each occurrence when used herein, H or C_{1-6} alkyl;

or a pharmaceutically acceptable derivative thereof;

for the preparation of a medicament for the treatment of cancer.

Preferred compounds of formula III include those in which:

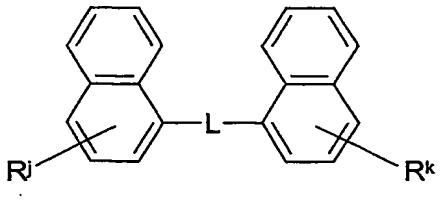
R^e represents $C(O)OR^g$ or $S(O)_2N(R^h)(R^i)$;

R^f represents one or two optional C_{1-2} alkyl (e.g. methyl) substituents;

R^g represents C_{1-3} alkyl (e.g. ethyl);

R^h and R^i independently represent C_{1-2} alkyl or, particularly, H.

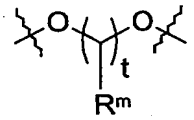
According to a fifth aspect of the invention there is provided the use of a compound of formula IV,



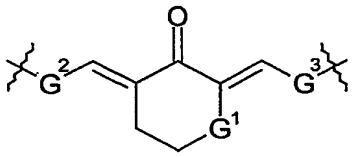
IV

wherein R^j and R^k independently represent one or more optional substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, nitro, cyano, halo and OC(O)aryl;

L represents a direct bond or a structural fragment of formula IVa or IVb,



IVa



IVb

wherein t represents 2, 3 or 4;

R^m represents, independently at each occurrence, H or C_{1-3} alkyl; and

G^1, G^2 and G^3 independently represent a direct bond or $(CH_2)_{1-2}$;

or a pharmaceutically acceptable derivative thereof;

for the preparation of a medicament for the treatment of cancer.

Preferred compounds of formula IV include those in which:

R^j and R^k are both absent or both represent OC(O)-(optionally substituted phenyl);

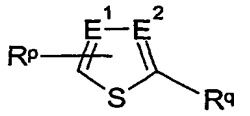
t represents 3 or, particularly, 2;

R^m represents, independently at each occurrence, methyl or, particularly, H;

G^1, G^2 and G^3 independently represent CH_2 or, particularly, a direct bond;

optional substituents on phenyl groups are one or more halo (e.g. chloro) atoms.

According to a sixth aspect of the invention there is provided the use of a compound of formula V,



V

wherein E^1 and E^2 independently represent CH or N;

R^p represents one to three optional substituents selected from C_{1-4} alkyl, halo, cyano, nitro, OH and SH;

R^q represents Het^x or SR^r;

Het^x represents a wholly aromatic or fully saturated five-membered heterocycle containing one or more heteroatoms selected from N, O and S, which heterocyclic group is optionally substituted by one or more substituents selected from C_{1-4} alkyl, halo, cyano, nitro, OH, =O and thienyl;

R^r represents C_{1-6} alkyl;

or a pharmaceutically acceptable derivative thereof;

for the preparation of a medicament for the treatment of cancer.

Preferred compounds of formula V include those in which:

E^1 and E^2 both represent CH or both represent N;

R^p represents one optional substituent selected from C_{1-2} alkyl, and, particularly, SH;

Het^x represents a wholly aromatic or fully saturated five-membered heterocycle containing one heteroatom selected from O and S, which heterocyclic group is optionally substituted by one substituent selected from =O and thienyl;

R^r represents optionally unsaturated C_{3-4} alkyl.

More preferred compounds of formula V include those in which:

when E^1 and E^2 both represent CH, then R^q represents Het^x;

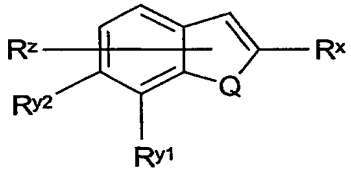
when E^1 and E^2 both represent N, then R^q represents SR^r;

R^p represents an optional SH substituent in the 2-position of the ring;

Het^x represents tetrahydrothiophenonyl (e.g. 5-tetrahydrothiophen-3-onyl) or thienyl (e.g. 2-thienyl), which latter group is optionally substituted by thienyl (e.g. 2-thienyl);

R^r represents unsaturated C_{3-4} alkyl (e.g. prop-2-ynyl).

According to a further aspect of the invention, there is provided the use of a compound of formula VI,



VI

wherein Q represents O, S or NH;

R^x represents $C(O)OR^{xa}$ or $C(O)N(R^{xb})R^{xc}$;

R^{y1} represents a substituent selected from halo, nitro and C_{1-6} alkyl, or R^{y1} and R^{y2} together form a fused benzene ring that is optionally substituted by R^z;

R^{y2} is absent or R^{y2} and R^{y1} together form a fused benzene ring that is optionally substituted by R^z;

R^z represents one or more optional substituents selected from halo, nitro, C_{1-6} alkyl and C_{1-6} alkoxy;

R^{xa} represents H, C_{1-6} alkyl, aryl or Het^{xa};

R^{xb} represents H, C_{1-6} alkyl, aryl or Het^{xb};

R^{xc} represents H or C_{1-6} alkyl;

Het^{xa} and Het^{xb} independently represent four- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from N, O and S, which heterocyclic groups are optionally substituted by one or more substituents selected from =O, OH, halo, nitro, cyano, C_{1-6} alkyl, aryl and NH_2;

wherein each aryl group, unless otherwise specified, is optionally substituted;

for the preparation of a medicament for the treatment of cancer.

Compounds of formula VI that may be mentioned include the compounds defined in respect of formula VI above, with the proviso that the compound of formula VI is not 7-nitro-1*H*-indole-2-carboxylic acid.

Compounds of formula VI that may also be mentioned include 7-nitro-1*H*-indole-2-carboxylic acid.

Preferred compounds of formula VI include those in which:
wherein Q represents S or NH;
R^x represents $C(O)OR^{xa}$;
R^{y1} represents a substituent selected from fluoro, chloro, nitro and trifluoromethyl, or R^{y1} and R^{y2} together form a fused benzene ring;
R^{y2} is absent or R^{y2} and R^{y1} together form a fused benzene ring;
R^z represents one or more optional substituents selected from halo, nitro, methyl, trifluoromethyl and methoxy;
R^{xa} represents H or phenyl, which latter group is optionally substituted by one to three substituents selected from halo, nitro and C_{1-4} alkyl (e.g. trifluoromethyl).

More preferred compounds of formula VI include those in which:
R^{y1} represents nitro, or R^{y1} and R^{y2} together form a fused benzene ring;
R^z is absent;
R^{xa} represents H or phenyl substituted by one or two halo (e.g. chloro) groups.

Pharmaceutically acceptable derivatives include salts and solvates. Salts which may be mentioned include acid addition salts.

Compounds of formulae I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V and VI may exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention.

Compounds of formulae I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V and VI may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, for example with a homochiral acid followed by separation of the diastereomeric esters by conventional means (e.g. HPLC, chromatography over silica). All stereoisomers are included within the scope of the invention.

For the avoidance of doubt, the compounds of formulae I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI need not be mammalian AP endonuclease inhibitors, but at least some of them (e.g. the compounds of the Figures and Tables, as defined hereinafter) may be. In this respect, preferred compounds of formulae I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI are those that are low molecular weight AP endonuclease inhibitors (e.g. inhibitors of Exo A, ExoIII, Rrp 1, Arp, Apn2, APEX, BAP1, rAPE, chAPE1, Ape2, hNTH1 and, particularly, HAP1). More preferred compounds of formulae I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI are

those that are low molecular weight mammalian AP endonuclease inhibitors, as hereinbefore defined (e.g. HAP1 inhibitors). Preferred low molecular weight AP endonuclease (e.g. HAP1) inhibitors include the compounds of the Figures and Tables, as defined hereinafter. Low molecular weight AP endonuclease (e.g. HAP1) inhibitors that may be mentioned include the compounds of Tables 1, 2a and 2b (i.e. compounds (i) to (clxxiii) of Claim 50). However, low molecular weight AP endonuclease (e.g. HAP1) inhibitors that may also be mentioned include the compounds of Table 2c (i.e. compounds (clxxiv) to (cxcii) of Claim 50).

According to a seventh aspect of the invention there is provided a method for treating cancer, which method comprises the administration of a low molecular weight mammalian AP endonuclease inhibitor, as hereinbefore defined, to a patient in need of cancer treatment.

According to a eighth aspect of the invention, there is provided a method for treating cancer, which method comprises the administration of a compound of formula I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI, as hereinbefore defined, to a patient in need of cancer treatment.

In addition to being useful in the treatment of cancer, compounds of formula I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI that inhibit AP endonucleases may be useful in the treatment of other diseases or conditions. For example, it is known that bacterial cells (e.g. *E. coli* cells) lacking the enzymes EndoIV and ExoIII are very sensitive to killing by nitric oxide (see, for example, E. J. Spek *et al. J. Bacteriology* 183(1), 131-138 (**2001**)). As this latter agent is produced by macrophages of the human immune system, inhibitors of AP endonuclease enzymes (such as EndoIV and ExoIII) may be useful as anti-microbial agents (e.g. anti-bacterial, anti-parasitic, anti-viral and/or anti-fungal agents).

It is believed that the susceptibility of mammalian cells to cell death may be increased by inhibiting the activity of a mammalian AP endonuclease enzyme. One manner of exploiting this susceptibility is to expose the same cells to agents that induce DNA damage. Thus, according to a preferred embodiment of the first aspect of the invention, there is provided the use of a low molecular weight mammalian AP endonuclease inhibitor, as hereinbefore defined, for the preparation of a medicament for the treatment of cancer in a patient who is administered a DNA damaging agent.

According to a preferred embodiment of any of the second, third, fourth, fifth or sixth aspects of the invention, there is provided the use of a compound of formula I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI, as hereinbefore defined, for the preparation of a medicament for the treatment of cancer in a patient who is administered a DNA damaging agent.

The term "is administered", when used herein, includes administration of the DNA damaging agent prior to, during and/or following treatment of the patient with the medicament that is prepared using a low molecular weight mammalian AP endonuclease inhibitor, or a compound of formula I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI (as appropriate). Administration of the DNA damaging agent preferably takes place within the period of 48 hours before and 48 hours after (e.g. within the period of 24 hours before and 24 hours after) treatment with this medicament. It is particularly preferred that administration takes place within the period of 12 hours before and 12 hours after (e.g. within the period of 6 hours before and 6 hours after) treatment, such as within the period of 3 hours before and 3 hours after treatment or within the period of 2 to 5 hours before treatment. Administration of multiple doses of the DNA damaging agent and/or the low molecular weight mammalian AP endonuclease inhibitor, or compound of formula I,

Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI are also contemplated. In such cases, the relative time scales mentioned above relate to the time separation between administration of neighbouring doses of DNA damaging agent and the low molecular weight mammalian AP endonuclease inhibitor or compound of formula I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI. For example, a single dose of the DNA damaging agent may be administered between two doses of low molecular weight mammalian AP endonuclease inhibitor or compound of formula I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI, which two doses are separated by up to 96 hours (e.g. by up to 24 hours, such as up to 6 hours). Further, administration of multiple doses of AP endonuclease inhibitor, or compound of formula I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI during a period of continuous administration of a DNA damaging agent (e.g. during continuous radiation therapy such as during brachytherapy or radioimmunotherapy) are also contemplated.

Where multiple doses of DNA damaging agent are administered, the agent may or may not be the same at each administration. Further, where multiple doses of the low molecular weight mammalian AP endonuclease inhibitor, or compound of formula I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI are administered, the inhibitor or compound may or may not be the same at each administration.

According to a preferred embodiment of the seventh aspect of the invention, there is provided a method of treating cancer, which method comprises administration of a low molecular weight mammalian AP endonuclease inhibitor, as hereinbefore defined, in combination with a DNA damaging agent to a patient in need of cancer treatment.

According to a preferred embodiment of the eighth aspect of the invention, there is provided a method of treating cancer, which method comprises

administration of a compound of formula I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI, as hereinbefore defined, in combination with a DNA damaging agent to a patient in need of cancer treatment.

The inventors believe that, by co-administering a low molecular weight mammalian AP endonuclease inhibitor, it may be possible to reduce the amount of DNA damaging agent used in cancer therapy. Thus, according to a further preferred embodiment of the seventh aspect of the invention, there is provided a method of treating cancer, which method comprises administering a reduced dose of DNA damaging agent in combination with a low molecular weight mammalian AP endonuclease inhibitor, as hereinbefore defined, to a patient in need of cancer treatment. In this aspect of the invention, the term "reduced dose" includes doses that are lower than the dose that would normally be administered to the selected patient (as determined by techniques known to those skilled in the art) and yet still produce (in combination with the mammalian AP endonuclease inhibitor) a broadly similar overall effect (e.g. the same overall effect) on the cancerous cells (i.e. a slowing in growth or a stabilisation or reduction in numbers). An advantage of reducing the dose of DNA damaging agent that is administered to a patient is that any cytotoxic side effects caused by the DNA damaging agent may be correspondingly reduced.

When used herein, the term "in combination with" includes administration of the DNA damaging agent before, at the same time as, and/or after administration of the low molecular weight mammalian AP endonuclease inhibitor or the compound of formula I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI. The term therefore includes the relative time scales for administration of single and multiple doses mentioned hereinbefore in relation to the term "is administered".

Where the low molecular weight mammalian AP endonuclease inhibitor or the compound of formula I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI is administered first to a patient, a number of different assay techniques may be used to determine the optimum time to administer the DNA damaging agent. For example, the activity level of a mammalian AP endonuclease enzyme in the patient (either in tumour or other tissue) may be monitored. In such cases, the DNA damaging agent may be administered once the mammalian AP endonuclease enzyme activity level drops below a predetermined value. Alternatively, the plasma concentration of the mammalian AP endonuclease inhibitor or compound of formula I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI may be monitored, in which case the DNA damaging agent may be administered at a predetermined point in the plasma concentration profile.

In order to monitor the effectiveness of any of the methods of cancer treatment according to the seventh and eighth aspects of the invention, the number and/or physical distribution of abasic sites may be monitored during and/or after treatment. Such monitoring may be achieved, for example, by using a suitable probe for abasic sites, such as that disclosed in Atamna, H. *et al. Proc. Natl. Acad. Sci. USA* 97(2), 686-691 (**2000**).

When used herein, the term "DNA damaging agent" includes all agents that induce the production of an AP site in DNA. Suitable DNA damaging agents include ionising radiation (e.g. subatomic particle radiation such as α-particles, β-particles, neutrons, protons, mesons and heavy ions or electromagnetic radiation such as high-frequency X-rays or gamma rays) and the following chemical agents.

(a) Alkylating agents including:

(i) nitrogen mustards such as mechlorethamine (HN_2), cyclophosphamide, ifosfamide, melphalan (L-sarcolysin) and chlorambucil;

(ii) ethylenimines and methylmelamines such as hexamethylmelamine, thiotepa;

(iii) alkyl sulfonates and thiosulfonates such as busulfan, methyl methanesulfonate (MMS) and methyl methanethiosulfonate;

(iv) nitrosoureas and nitrosoguanidines such as carmustine (BCNU), lomustine (CCNU), semustine (methyl-CCNU), streptozocin (streptozotocin) and *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG); and

(v) triazenes such as dacarbazine (DTIC; dimethyltriazenoimidazole-carboxamide).

(b) Antimetabolites including:

(i) pyrimidine analogues such as fluorouracil (5-fluorouracil; 5-FU), floxuridine (fluorodeoxyuridine; FUdR) and cytarabine (cytosine arabinoside); and

(ii) purine analogues and related inhibitors such as mercaptopurine (6-mercaptopurine; 6-MP), thioguanine (6-thioguanine; TG) and pentostatin (2'-deoxycoformycin).

(c) Natural Products including:

(i) epipodophyllotoxins such as etoposide and teniposide; and

(ii) antibiotics such as dactinomycin (actinomycin A, C, D or F), daunorubicin (daunomycin; rubidomycin), doxorubicin, bleomycin, plicamycin (mithramycin) and mitomycin (mitomycin A, B or C).

(d) Miscellaneous agents including:

(i) platinum coordination complexes such as cisplatin (*cis*-DDP) and carboplatin;

(ii) anthracenedione such as mitoxantrone and anthracycline;

(iii) substituted urea such as hydroxyurea;

(iv) methyl hydrazine derivatives such as procarbazine (N-methylhydrazine, MIH);

(v) photoactivatable compounds (e.g. psoralens); and

(vi) DNA topoisomerase inhibitors (e.g. m-amsacrine and camptothecin).

When the DNA damaging agent and the low molecular weight mammalian AP endonuclease inhibitor or compound of formula I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI are administered at the same time, they may either be co-administered as separate formulations or administered together in a single, combined formulation.

Thus, according to a ninth aspect of the invention there is provided the use of a combination of a chemical DNA damaging agent and a low molecular weight mammalian AP endonuclease inhibitor, as hereinbefore defined, or a compound of formula I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI, as hereinbefore defined, in the manufacture of a medicament for the treatment of cancer. Thus, the chemical DNA damaging agent and the low molecular weight mammalian AP endonuclease inhibitor or a compound of formula I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI may be combined in the same medicament before administration to the patient.

For the avoidance of doubt, the term "chemical DNA damaging agent" has the same meaning as "DNA damaging agent", as hereinbefore defined, except that it does not include non-chemical agents such as ionising radiation.

The term "cancer", when used herein, will be well understood by those skilled in the art, and includes any form of malignancy or premalignancy.

Cancers that may be mentioned include those that demonstrate enhanced expression of DNA repair enzymes, such as the human carcinoma cell lines described in: Lai *et al. Biochem. Pharmacol.* 37, 4597-4600 (**1988**); Hospers *et al. Cancer Res.* 48, 6803-6807 (**1988**); Masuda *et al. Cancer Res.* 48, 5713-5716 (**1988**); Kraker *et al. Cancer Lett.* 38, 307-314 (**1988**); and Scanlon *et al. Anticancer Res.* 9, 1301-1312 (**1989**), the disclosures of which documents are hereby incorporated by reference. Further cancers that may be mentioned include leukemias, lymphomas, myelomas, neuroblastomas, neoplasias of bladder, testicular, edometrial, gastric or lung origin neoplasias. Particular cancers that may be mentioned include the following neoplasias: Hodgkin's, non-Hodgkin's and Burkitt's lymphomas; myelomas; glioblastomas, medulloblastomas and neuroblastomas; pancreatic islet cell carcinomas; osteogenic sarcoma; breast, endometrial, testicular, cervical, gastric, squamous cell, adrenocortical and small cell lung carcinomas and the like.

In any of the foregoing aspects of the invention, where a low molecular weight mammalian AP endonuclease inhibitor, a compound of formula I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI, and/or a chemical DNA damaging agent (as appropriate), or a medicament prepared therefrom, is administered to a patient, these components or medicaments will normally be administered orally, subcutaneously, intravenously, intraarterially, transdermally, intranasally, by inhalation, or by any other parenteral route, in the form of pharmaceutical preparations comprising the relevant active ingredient(s) either as such or in the form of (a) non-toxic organic or inorganic acid or base addition salt(s), in (a) pharmaceutically acceptable dosage form(s). Depending upon the disorder and patient to be treated, as well as the route of administration, the components or medicaments may be administered at varying doses.

In any of the foregoing aspects of the invention, where a DNA damaging agent that is radiation is administered to a patient, it may be administered by any method known to those skilled in the art. Such methods include administration by:

1) external beam (e.g. targeted X-ray source);
2) brachytherapy (i.e. sealed or unsealed sources inserted into or near the tumour site); and
3) targeted therapy (e.g. radioimmunotherapy using, for example, a radiolabelled antibody).

According to tenth aspect of the invention there is provided a composition comprising:

(a) a chemotherapeutic agent; and
(b) a low molecular weight mammalian AP endonuclease inhibitor, as hereinbefore defined, or a compound of formula I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI, as hereinbefore defined.

The term "chemotherapeutic agent", when used herein includes any compound that can be used to treat cancer. The term thus includes the following agents.

(a) Alkylating agents including:
    (i) nitrogen mustards such as mechlorethamine (HN_2), cyclophosphamide, ifosfamide, melphalan (L-sarcolysin) and chlorambucil;
    (ii) ethylenimines and methylmelamines such as hexamethylmelamine, thiotepa;
    (iii) alkyl sulfonates and thiosulfonates such as busulfan, methyl methanesulfonate (MMS) and methyl methanethiosulfonate;
    (iv) nitrosoureas and nitrosoguanidines such as carmustine (BCNU), lomustine (CCNU), semustine (methyl-CCNU), streptozocin

(streptozotocin) and *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG); and

(v) triazenes such as dacarbazine (DTIC; dimethyltriazenoimidazole-carboxamide).

(b) Antimetabolites including:

(i) folic acid analogues such as methotrexate (amethopterin);

(ii) pyrimidine analogues such as fluorouracil (5-fluorouracil; 5-FU), floxuridine (fluorodeoxyuridine; FUdR) and cytarabine (cytosine arabinoside); and

(iii) purine analogues and related inhibitors such as mercaptopurine (6-mercaptopurine; 6-MP), thioguanine (6-thioguanine; TG) and pentostatin (2'-deoxycoformycin).

(c) Natural Products including:

(i) vinca alkaloids such as vinblastine (VLB) and vincristine;

(ii) epipodophyllotoxins such as etoposide and teniposide;

(iii) antibiotics such as dactinomycin (actinomycin A, C, D or F), daunorubicin (daunomycin; rubidomycin), doxorubicin, bleomycin, plicamycin (mithramycin) and mitomycin (mitomycin A, B or C);

(iv) enzymes such as L-asparaginase; and

(v) biological response modifiers such as interferon alphenomes.

(d) Miscellaneous agents including:

(i) platinum coordination complexes such as cisplatin (*cis*-DDP) and carboplatin;

(ii) anthracenedione such as mitoxantrone and anthracycline;

(iii) substituted urea such as hydroxyurea;

(iv) methyl hydrazine derivatives such as procarbazine (N-methylhydrazine, MIH);

(v) adrenocortical suppressants such as mitotane (*o,p'*-DDD) and aminoglutethimide;

(vi) taxol and analogues/derivatives;

(vii) hormone agonists/antagonists such as flutamide and tamoxifen;

(viii) photoactivatable compounds (e.g. psoralens);

(ix) DNA topoisomerase inhibitors (e.g. m-amsacrine and camptothecin);

(x) anti-angiogenesis agents (e.g. SU6668, SU5416, combretastatin A4, angiostatin and endostatin); and

(xi) immunotherapeutic agents (e.g. radiolabelled antibodies such as Bexxar™ and Theragyn™ (Pemtumomab™)).

According to a preferred embodiment of the tenth aspect of the invention, there is provided a composition comprising:

(a) a chemical DNA damaging agent, as hereinbefore defined; and

(b) a low molecular weight mammalian AP endonuclease inhibitor, as hereinbefore defined, or a compound of formula I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI, as hereinbefore defined.

The low molecular weight mammalian AP endonuclease inhibitors of the present invention may also be used in alternative methods of treating cancer, such as gene therapy (wherein the "therapeutic" DNA may be provided in "naked" form (i.e. as a solution or suspension), "packaged" in the interior of a liposome or as part of a virus particle). Thus the invention also encompasses compositions comprising:

(a) a source of therapeutic DNA (e.g. the sources mentioned above); and

(b) a low molecular weight mammalian AP endonuclease inhibitor, as hereinbefore defined, or a compound of formula I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI, as hereinbefore defined.

It is known that mammalian AP endonuclease enzymes are involved in the cellular protection of tumour cells against hypoxic stress (see, for example,

Walker *et al. Nucleic Acids Research* 22(23), 4484-4489 (**1994**)). Thus, in another preferred embodiment of the tenth aspect of the invention, there is provided a composition comprising:

(a) an anti-angiogenesis agent, as hereinbefore defined; and

(b) a low molecular weight mammalian AP endonuclease inhibitor, as hereinbefore defined, or a compound of formula I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI, as hereinbefore defined.

The composition according to the tenth aspect of the invention may be used in the practice of the seventh or the eighth aspect of the invention. Thus, an eleventh aspect of the invention provides a composition according to the tenth aspect of the invention for use in medicine.

Typically, the composition according to the tenth aspect of the invention further comprises a pharmaceutically acceptable carrier. Thus, a twelfth aspect of the invention provides a pharmaceutical composition (or formulation as it may be termed) comprising:

(a) a chemotherapeutic agent;

(b) a low molecular weight mammalian AP endonuclease inhibitor, as hereinbefore defined, or a compound of formula I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI, as hereinbefore defined; and

(c) a pharmaceutically acceptable carrier.

The carrier(s) must be "acceptable" in the sense of being compatible with the composition of the invention and not deleterious to the recipients thereof. Typically, the carriers will be water or saline which will be sterile and pyrogen free.

According to thirteenth aspect of the invention there is provided a therapeutic system (or, as it may be termed, a kit of parts) comprising:

(a) a chemotherapeutic agent, as hereinbefore defined; and

(b) a low molecular weight mammalian AP endonuclease inhibitor, as hereinbefore defined, or a compound of formula I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI, as hereinbefore defined.

The therapeutic system or kit of parts may suitably contain components (a) and (b) packaged and presented in suitable formulations for use in combination, either for administration simultaneously or for administration which is separated in time.

Preferred embodiments of the twelfth and thirteenth aspects of the invention include those in which the chemotherapeutic agent is a chemical DNA damaging agent, as hereinbefore defined.

The compositions according to the tenth aspect of the invention, and the separate components of the therapeutic system according to the thirteenth aspect of the invention will normally be administered orally, subcutaneously, intravenously, intraarterially, transdermally, intranasally, by inhalation, or by any other parenteral route, in the form of pharmaceutical preparations comprising the relevant active ingredient(s) either as such or in the form of (a) non-toxic organic or inorganic acid or base addition salt(s), in (a) pharmaceutically acceptable dosage form(s). Depending upon the disorder and patient to be treated, as well as the route of administration, the compositions or separate components of the therapeutic systems may be administered at varying doses.

The compositions according to the tenth aspect of the invention, and the separate components of the therapeutic system according to the thirteenth aspect of the invention are preferably formulated for use in medicine (e.g. in admixture with a pharmaceutically acceptable adjuvant, diluent and/or

carrier). Such formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the relevant active ingredient(s) with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient(s) with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations in accordance with the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g. sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethylcellulose in varying proportions to provide desired release profile.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavoured basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouth-washes comprising the active ingredient in a suitable liquid carrier.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

Suitable doses of low molecular weight mammalian AP endonuclease inhibitors, compounds of formula I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or

VI, and/or (chemical) DNA damaging agents (as appropriate), in any of the above-mentioned cancer treatments may be determined routinely by the medical practitioner or other skilled person (for example by utilising data from pharmacological studies and preclinical animal models).

As well as being useful in the treatment of cancer, inhibition of mammalian AP endonucleases may also be desirable in other circumstances (see, for example, Evans, A.R. *et al. Mutation Research* 461, 83-108 (**2000**)). For example, patients suffering from chronic inflammatory and oxyradical overload diseases (such as ulcerative colitis, viral hepatitis, Wilson disease, haemochromatosis, chronic gastritis, chronic pancreatitis and Barret oesophagus), which conditions are linked with an increased susceptibility to cancer, may benefit from the administration of a mammalian AP endonuclease inhibitor. Also, inhibition of mammalian AP endonucleases may be desirable in the treatment of Alzheimer's disease, which is associated with senile plaques, plaque-like structures and areas of brain injury that demonstrate elevated HAP1 expression (see Tan, Z. *et al. Neuroreport* 9(12), 2749-2752 (**1998**)). Furthermore, administration of a mammalian AP endonuclease inhibitor in combination with a DNA damaging agent such as ionising radiation (e.g. gamma radiation from ^{192}Ir) may be useful in the prevention of restenosis (see, for example Katuza, G. Z. *et al. Catheterization and Cardiovascular Interventions* 52, 518-529 (**2001**), the disclosures of which document are hereby incorporated by reference).

Thus, according to an fourteenth aspect of the invention there is provided the use of a low molecular weight mammalian AP endonuclease inhibitor, as hereinbefore defined, for the preparation of a medicament for the treatment of a condition where inhibition of a mammalian AP endonuclease enzyme (e.g. HAP1) is required or desired.

Similarly, according to a fifteenth aspect of the invention, there is provided a method of inhibiting a mammalian AP endonuclease (e.g. HAP1), which method comprises administering a low molecular weight mammalian AP endonuclease inhibitor, as hereinbefore defined.

According to a preferred embodiment of the fifteenth aspect of the invention there is provided a method of inhibiting a mammalian AP endonuclease (e.g. HAP1), which method comprises administering a low molecular weight mammalian AP endonuclease inhibitor, as hereinbefore defined, to a patient who has a condition where inhibition of a mammalian AP endonuclease (e.g. HAP1) is required or desired.

For the fourteenth and fifteenth aspects of the invention, routes of administration, types of formulation and so on are the same as for any of the foregoing aspects of the invention.

An alternative utility for the mammalian AP endonuclease inhibitors defined herein is in the production of mammalian (preferably human) cells which can be used in mutagenicity testing. That is, test cells (preferably of human origin) may be generated by contacting them with one or more of the mammalian AP endonuclease inhibitors defined herein. The present invention then also includes the use of such test cells either:

(a) in a method of detecting the mutagenic, cytotstatic or cytotoxic nature of a test compound, by, in those test cells, monitoring the frequency of phenotypic change, the cell proliferation or the frequency of cell death (as appropriate) in the presence and absence of said test compound; or

(b) in a method of assessing the ability of a test compound to protect against DNA damage, by monitoring the frequency of DNA damage,

in the presence and absence of said test compound, in groups of test cells that have been contacted with a known carcinogen.

As the crystal structures of HAP1 and other AP endonuclease enzymes are known (see, for example Barzilay, G. *et al. Nature Structural Biology* 2(7), 561-567 (**1995**) or Gorman *et al. EMBO J.* 16, 6548-6558 (**1997**)), compounds that are known to inhibit AP endonucleases (e.g. compounds of formulae I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI that inhibit AP endonucleases, such as the compounds of the Figures and Tables, as defined hereinafter) may be analysed in relation to such crystal structures. Using the results of such analyses, modifications of the structures of existing inhibitors, aimed at producing new and more potent inhibitors of AP endonucleases, may be proposed. Methods of identifying compounds by structure-based drug design are known to those skilled in the art (see, for example, Gane, P. J. and Dean, P. M. *Engineering and Design* 401-404 (**2000**)). AP endonuclease inhibitors identified by such methods are also considered to be within the scope of the present invention.

Similarly, according to a sixteenth aspect of the invention, there is provided the use of a compound of the Figures and Tables, as defined hereinafter, as a lead compound in the identification of a low molecular weight AP endonuclease inhibitor (e.g. a mammalian AP endonuclease inhibitor such as an inhibitor of HAP1).

The term "lead compound" is well known to those skilled in the art, and may include the meaning that the agent, whilst itself may or may not be suitable for use as a drug (for example it may not be suitable because it is insufficiently potent against its intended target, insufficiently selective in its action, unstable, poorly soluble, difficult to synthesise or has poor

bioavailability) may provide a starting-point for the design of other compounds that may have more desirable characteristics.

The use of the compounds as lead compounds includes their use as positive controls in assays (whether *in vitro* or cell based) in which further compounds are tested for their ability to inhibit an AP endonuclease. Thus, one embodiment of this aspect of the invention provides a method of determining whether a test compound is to be selected for further study, the method comprising determining whether the test compound has AP endonuclease inhibitor activity and comparing any such activity with the inhibitor activity of the said lead compounds. Compounds are typically selected for further study if they inhibit AP endonuclease activity to the same or a greater extent than the lead compound.

A further embodiment of this aspect of the invention provides a method of determining whether a test compound is to be selected for further study, the method comprising determining a pharmacological characteristic of the test compound and comparing it with the said pharmacological characteristic of the lead compound. Compounds are selected which have the pharmacological characteristic which is as good as or better than the lead compound. Pharmacological characteristics which may be tested for include potency, selectivity, stability, solubility and bioavailability.

It will be appreciated that for the above two embodiments, the inhibitor or pharmacological characteristics of the lead compound and the test compound need not be determined at the same time. Suitably, the characteristics of the lead compound are present in a look-up table, for example certain AP endonuclease inhibitory activity of the lead compounds is given herein.

A still further embodiment of this aspect of the invention is the design or selection of test compounds based on the lead compounds described herein. Thus, this embodiment provides a method of designing or selecting a test compound based on the structure of the lead compound. Typically, the structure of the lead compound is studied by a medicinal chemist and test compounds are designed or selected based on one or more of the following criteria: (1) structural similarity to the lead compound, (2) ease of chemical synthesis, (3) predicted solubility or bioavailability, (4) molecular modelling using the structure of the lead compound and the three-dimensional structure of its target (e.g. HAP1 or other AP endonuclease, the crystal structures of which are known; see above).

It will be appreciated that at least some test compounds fall within the general formulae of the compounds of formulae I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V and VI. Thus a further aspect of the invention provides a method of determining the AP endonuclease inhibitory and/or pharmacological properties of a compound selected from the compounds of formulae I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V and VI.

In any of the seventh and subsequent aspects of the invention mentioned above, references to compounds of formulae I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V and/or VI include, in particular, references to compounds of formulae I, Ia, Ib, IIa, IIb, III, IV and/or V, as well as separately to compounds of formulae Ic, IIc, IId and/or VI.

Preparation

Compounds of formulae I, Ia, Ib, Ic, IIa, IIb, IIc, IId, III, IV, V or VI, and derivatives thereof, are either commercially available, are known in the literature, or may be obtained by conventional synthetic procedures, in

accordance with standard techniques, from readily available starting materials using appropriate reagents and reaction conditions, for example as described in any of March, J "*Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*", 3rd Ed., John Wiley & Sons, New York (1985), "*Comprehensive Organic Transformations - A Guide to Functional Group Preparations*", Larrock, R. C., VCH (1989), "*Houben-Weyl Methods of Organic Chemistry*" Schaumann, E. and Kreher, R. (Eds.), Thieme, Stuttgart, "*Comprehensive Heterocyclic Chemistry II*" Katritsky, A. R.; Rees, C. W.; and Scriven, E. F. V (Eds.), 1st Edition, Elsevier Science Ltd. (1996) or Buckingham, J.; Macdonald, F.; and Buckingham, J. "*The Dictionary of Organic Compounds*" Heilbron, Sir I. (Ed), 6th Edition, Chap. & H., England (1995).

Biological Tests

Test A (Cell based Assay)

Freshly harvested and trypsinised MCF7 tumor cells in E7 tissue culture media plus 10% fetal calf serum (Gibco BRL, UK) are seeded into 96-well flat-bottom tissue culture plate (Falcon) at approximately 20,000 cells per well. Cells are incubated overnight in humidified containers in a cell culture incubator (5% CO_2) at 37°C.

In a separate 96 well plate (dilution plate), medium containing MMS (Methyl methanesulfonate, Aldrich), titered to give either a range of toxic effects (e.g. 10 to 10000 μg/mL) or a single sub-toxic effect (e.g. 100 μg/mL), plus and minus test compounds are prepared in E7 plus 5% fetal calf serum.

Medium containing 10% fetal calf serum is aspirated from cells, taking care not to disturb the growing monolayer and 0.15 mL media including MMS

plus and minus test compounds is transferred from the dilution plate to the assay plate. Cells are then incubated for 16 hours in humidified containers in a cell culture incubator (5%CO_2) at 37°C.

Trichloroacetic acid (0.05 mL of a 50% (w/w) aqueous solution) is added per well and the plate incubated for 1 hour at 4°C. The following washes and incubations are performed at room temperature.

(i) Wash plate (x5) with distilled water remove residual water and allow to air dry.

(ii) Add 0.1 mL per well 0.1% (w/v) sulforhodamine B (Sigma, UK) in 1% (v/v) acetic acid and incubate for 30 min.

(iii) Wash (x4) with 1% acetic acid, remove residual liquid and allow to air dry.

Solubilise bound dye by adding 0.1 mL per well of 10 mM Tris base pH 10.5 and gently shaking the plate for 5 minutes. Measure the absorbance of each well at 492 nm in a microplate reader. The absorbance value registered is a measure of cell survival per well.

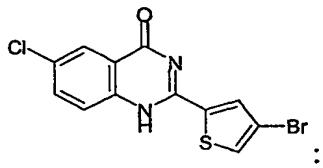
Description of the Figures and Tables

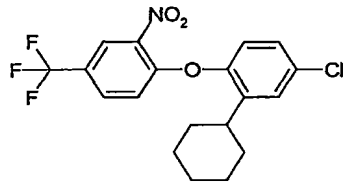
Figure 1

Figure 1 shows the survival of MCF7 tumor cells (as measured by absorbance at 492 nm - see Test A above) at various concentrations of methyl methanesulfonate (MMS) in the presence and absence of low molecular weight mammalian AP endonuclease inhibitors.

Apparent IC_{50} values for MMS in the presence and absence of the various inhibitors, calculated from the cell survival curves, are as follows

(a) MMS alone: 900 μg/mL

(b)  : 200 μg/mL

(c)  : 190 μg/mL

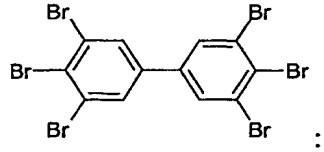
(d)  : 200 μg/mL

Figure 2

Figure 2 shows, for various low molecular weight mammalian AP endonuclease inhibitors, the percentage survival (relative to survival in culture medium alone) of MCF7 tumor cells (see Test A above) in the presence of:

(i) inhibitor alone;

(ii) MMS alone; and

(iii) inhibitor and MMS together.

Cells were exposed to the inhibitors at the concentrations indicated for 16 hours. When used, MMS was present at a sublethal concentration calculated to give approximately 60-70% cell survival.

Table 1

Table 1 contains the following results for each of the compounds there listed.

1) A HAP1 IC_{50} value (expressed in μM), as calculated from HAP1 AP endonucleolytic activity levels determined at different concentrations of inhibitor (which activity levels may be measured, for example, by an assay such as that described in Example 1 below or in Barzilay, G. *et al. Nature Structural Biology* 2(7), 561-567 (**1995**), using the oligonucleotide disclosed therein or an oligonucleotide comprising the following sequence

```
5'  GCCCCCXGGGGACGTACGATATCCCGCTCC  3'
3'  CGGGGGCCCCCTGCATGCTATAGGGCGAGG  5'
```

where **X** represents an abasic site; this oligonucleotide may be prepared by methods known to those skilled in the art, such as those described in the Barzilay, G. *et al.* article mentioned above).

2) An ExoIII IC_{50} value (expressed in μM), as calculated from ExoIII AP endonucleolytic activity levels determined at different concentrations of inhibitor (which activity levels may be determined, for example, in an analogous manner to the determination of activity levels of HAP1, as described above).

3) An indication of the endonucleolytic activity of HpaII in the presence of a 5 μM concentration of inhibitor, expressed as percentage inhibition of the reaction rate in the absence of inhibitor (where HpaII activity may be determined, for example, by an assay that utilises a plasmid containing a single HpaII cleavage site, wherein the production of linear cleavage products over time is measured by gel

based electrophoresis under conditions known to those skilled in the art).

Table 2a

Table 2a contains the following results for compounds there listed.

1) The AP endonucleolytic activity of HAP1 in the presence of a 20 μM concentration of inhibitor, expressed as a percentage of the reaction rate in the absence of an inhibitor (wherein HAP1 activity may be determined, for example, as described above).

2) A HAP1 IC_{50} value (expressed in μM), determined as described above in connection with Table 1.

3) An ExoIII IC_{50} value (expressed in μM), determined as described above in connection with Table 1.

Table 2b

Table 2b contains the following results for compounds there listed.

1) The AP endonucleolytic activity of HAP1 in the presence of a 5 μM concentration of inhibitor, expressed as a percentage of the reaction rate in the absence of an inhibitor (wherein HAP1 activity may be determined, for example, as described above).

2) A HAP1 IC_{50} value (expressed in μM), determined as described above in connection with Table 1.

3) An ExoIII IC_{50} value (expressed in μM), determined as described above in connection with Table 1.

Table 2c

Table 2c contains the following results for compounds there listed.

1) A HAP1 IC_{50} value (expressed in μM), determined as described above in connection with Table 1.

2) An ExoIII IC_{50} value (expressed in μM), determined as described above in connection with Table 1.

Examples

The compounds listed in Figures 1 and 2 as well as those listed in Tables 1, 2a, 2b and 2c were all obtained from Maybridge plc. (Trevillet, Tintagel, Cornwall PL34 0HW, England).

The enzyme ExoIII was obtained from Promega (Delta House, Chilworth Research Centre, Southampton SO16 7NS, UK) and the enzyme HpaII was obtained from New England Biolabs (32 Tozer Road, Beverly, MA 01915-5599, USA). The enzyme HAP1 may be obtained from Trevigen Ltd. Gaithersburg, MD, USA.

Example 1

The compounds of Tables 1, 2a, 2b and 2c were all found to inhibit the endonucleolytic activity of HAP1, as may be determined by an assay such as that described in Barzilay, G. *et al. Nature Structural Biology* 2(7), 561-567 (**1995**), or by the following assay method.

(1) Production and purification of human AP endonuclease.

A peT 28 vector carrying the HAP-1 cDNA with codons to encode a 'C-terminal hexahistidine tag' was transformed into *E. coli* BL-21 cells. After transformation, the cells were induced with 0.4 mM IPTG for 2 hours at 37°C. HAP-1 was purified from the cell extracts by nickel chelation chromatography (Bio Cad) and heparin affinity chromatography (Bio Cad). Presence of HAP-1 was confirmed by western blotting. The amount of HAP-1 was quantified using a Bio-Rad protein assay. The amount of HAP-1 was quantified to 125 ng/μL and the protein was judged to be >95% pure.

(2) Synthesis of reduced abasic sites in oligonucleotides.

To mimic an in vivo system, an uracil containing 18-mer oilgonucleotide CTCGCAAGUGGGTACCGA and its complementary oligonucleotide TCGGTACCCGCTTGCGAG were synthesised. The uracil containing oligonucleotide was 5' end labelled with [γ-^{32}P]-ATP. Equimolar concentrations of radiolabelled oligonucleotide and its complementary oligonucleotide were annealed in a reaction containing 0.1 M Potassium chloride, incubated at 90°C for 5 minutes and then cooled at room temperature for 15 minutes. Abasic sites were created by adding uracil glycosylase (UDG concentration 60 ng/μL and 1 unit UDG acts on 0.5 μg of DNA) to the above reaction and the mixture incubated at 37°C for one hour. Sodium borohydride ($NaBH_4$) at a final concentration of 0.1 M was subsequently added, and the mixture was incubated on ice for 30 minutes. This generated 'reduced and stable' abasic sites. The above mixture was spun through a G-50 column to remove salt.

(3) HAP-1 cleavage reaction.

A base excision reaction buffer was made containing 40 mM Hepes-KOH (pH 7.8), 5 mM $MgCl_2$, 0.5 mM DTT (Dithiothreitol) and 0.1 mM EDTA. A HAP-1 cleavage reaction was set up as follows.

Substrate DNA = 1 μL (750 picograms)

Buffer = 8 μL

HAP-1 = 1 μL

The above mixture was incubated at 37°C for 30-60 minutes. 1 μL of bromo phenol blue containing stop buffer [50% glycerol, 10 mM Tris HCl, pH 8.0, 1mM EDTA, 0.1% Bromo Phenol Blue and 0.1% Xylene Cyanol] was added at the end of the reaction and sample was denatured at 90-100°C for 2 minutes. The sample was then run in a 10% TBE gel [10% denaturing polyacrylamide gel] and imaged using a phosphorImager analysis (Molecular Dynamics). The optimal amount of HAP-1 required for the reaction was found to be 0.125 ng (by serial dilution) in a 10 μL reaction.

(4) HAP-1 inhibitor assay.

A concentration range of 100 μM - 0.01 μM of the potential HAP-1 inhibitors were used to set up an assay as follows, i.e., 100 μM, 30 μM, 10 μM, 3 μM, 1 μM, 0.3 μM, 0.1 μM, 0.03 μM, 0.01 μM.

Substrate DNA = 1 μL (as above)

Buffer = 7 μL

HAP-1 = 1 μL

Compound = 1 μL

The above mixture was incubated at 37°C for 30-60 minutes. 1 μL of stop buffer was added at the end of the reaction and sample was denatured at 90-100°C for 2 minutes. The sample was run in a 10% TBE gel and imaged using a phosphorImager analysis (Molecular Dynamics).

Example 2

MCF-7 Tumour cell survival rates in the presence MMS and the presence and absence of compounds listed in Table 1 were measured (see Test A above). Percentage cell survival was decreased when compounds listed in Table 1 were present.

Example 3

Protocol for combination therapy.

Radiotherapy

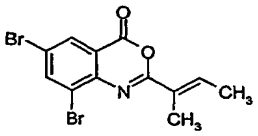
An effective dose (which may be determined by methods known to those skilled in the art) of a low molecular weight AP endonuclease (e.g. HAP1) inhibitor is administered to a patient in need of cancer treatment. Between 30 and 300 minutes following such administration, the patient then undergoes conventional radiotherapy.

Table 1

Examples of inhibitors of Hap1 (relevant generic formulae given in brackets) and their calculated IC_{50} vs. Hap1 (μM) and ExoIII (μM).

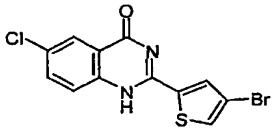
All compounds show <20% inhibition of the control rate of the restriction enyzme Hpa II at 5 μM except those marked * (20-80% inhibition) and ** (>80% inhibition).

6,8-Dibromo-2-(1-methyl-propenyl)-benzo[d][1,3]oxazin-4-one (IIa)



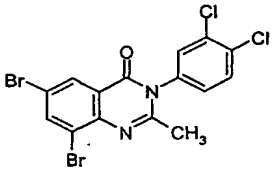
HAP1	9.8
EXO III	19.4
HPA II	< 20%

2-(4-Bromo-thiophen-2-yl)-6-chloro-1H-quinazolin-4-one (IIb)



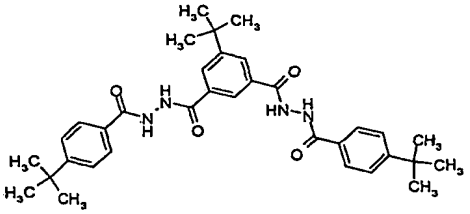
HAP1	4.5
EXO III	200
HPA II	< 20%

6,8-Dibromo-3-(3,4-dichloro-phenyl)-2-methyl-3H-quinazolin-4-one (IIa)



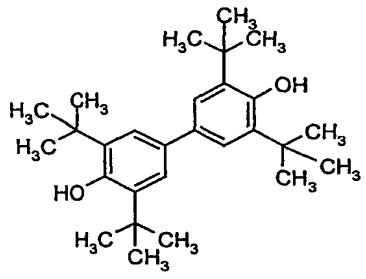
HAP1	14.9
EXO III	545.5
HPA II	< 20%

N-[(4-tert-butyl-benzoyl)-amino]-3-tert-Butyl-5-[N'-(4-tert-butyl-benzoyl)-hydrazinocarbonyl]-benzamide (Ia)



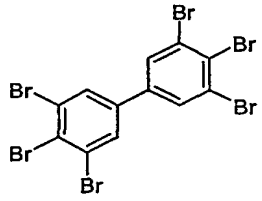
HAP1	9.9
EXO III	558.6
HPA II	< 20%

3,5,3',5'-Tetra-tert-butyl-biphenyl-4,4'-diol (Ia)



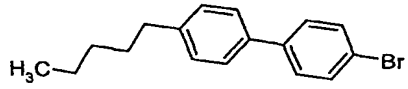
HAP1	5
EXO III	10.3
HPA II	< 20%

3,4,5,3',4',5'-Hexabromo-biphenyl (Ia)



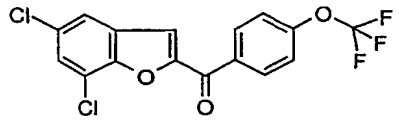
HAP1	0.2
EXO III	9.4
HPA II	< 20%

4'-Bromo-4-pentyl-biphenyl (Ia)



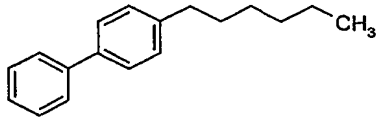
HAP1	4.1
EXO III	18.2
HPA II	< 20%

(5,7-Dichloro-benzofuran-2-yl)-(4-trifluoromethoxy-phenyl)-methanone (IIb)



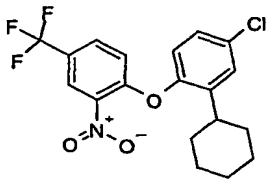
HAP1	8.7
EXO III	7
HPA II	< 20%

4-Hexyl-biphenyl (Ia)



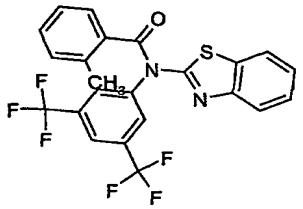
HAP1	7.8
EXO III	11.9
HPA II	< 20%

Oxa-[(4-chloro-2-cyclohexyl)phenyl]-2-nitro-4-trifluoromethyl-phenol (Ia)



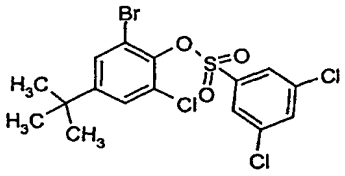
HAP1	4.6
EXO III	15
HPA II	< 20%

N-Benzothiazol-2-yl-N-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-benzamide (Ia)



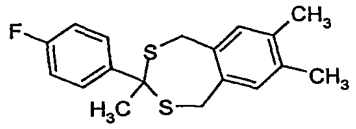
HAP1	14.3
EXO III	185.9
HPA II	< 20%

3,5-Dichloro-benzenesulfonic acid 2-bromo-4-tert-butyl-6-chloro-phenyl ester (Ia)



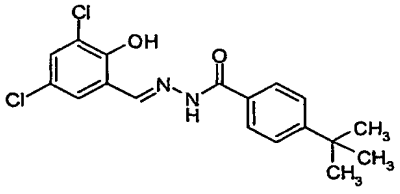
HAP1	4.1
EXO III	24.8
HPA II	< 20%

3-(4-Fluorophenyl)-3,7,8-trimethyl-1,5-dihydrobenzo[e][1,3]dithiepine (Ib)



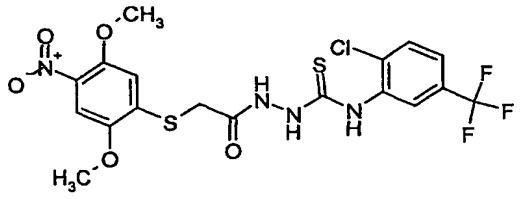
HAP1	26.8
EXO III	43.9
HPA II	< 20%

4-tert-Butylbenzoic acid (3,5-dichloro-2-hydroxybenzylidene)hydrazide (Ia)



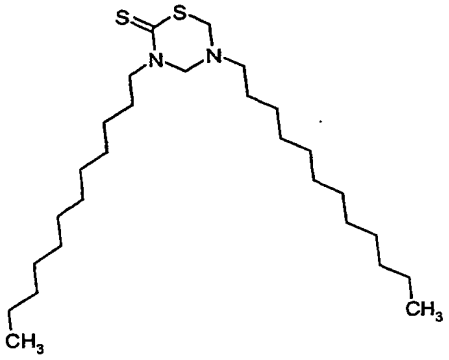
HAP1	5.2
EXO III	8.6
HPA II	< 20%

2,5-Dimethoxy-4-nitro-thia-(N'[N-(2-chloro-5-trifluoromethyl)phenyl)-thiocarboxyamino]hyrazinecarbonylmethyl]phenol (Ia)



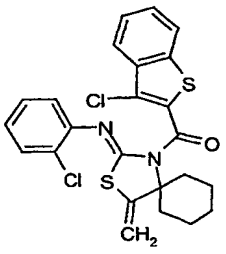
HAP1	65.3
EXO III	706.8
HPA II	< 20%

3,5-Didodecyl-[1,3,5]thiadiazinane-2-thione (none)



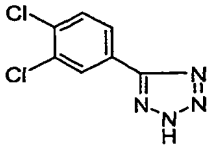
HAP1	5.2
EXO III	12
HPA II	>80% **

(3-Chloro-benzo[b]thiophen-2-yl)-[2-(2-chloro-phenylimino)-4-methylene-3-thia-1-aza-spiro[4.5]dec-1-yl]-methanone (Ib)



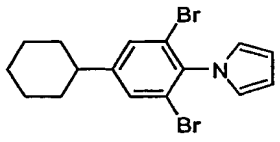
HAP1	1.4
EXO III	52.7
HPA II	20-80% *

5-(3,4-Dichloro-phenyl)-2H-tetrazole (Ib)



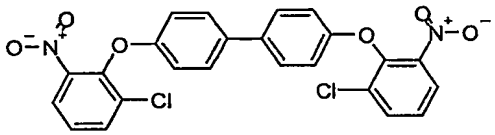
HAP1	8.8
EXO III	11.3
HPA II	< 20%

1-(2,6-Dibromo-4-cyclohexyl-phenyl)-1H-pyrrole (Ib)



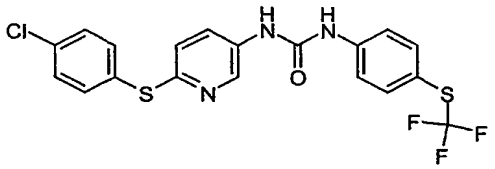
HAP1	4.7
EXO III	21
HPA II	< 20%

4,4'-Bis-(2-chloro-6-nitro-phenoxy)-biphenyl (Ia)



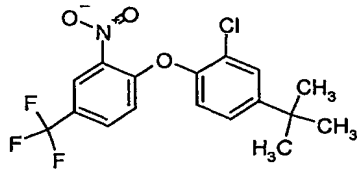
HAP1	2.9
EXO III	17.5
HPA II	20-80%*

1-[6-(4-Chloro-phenylsulfanyl)-pyridin-3-yl]-3-(4-trifluoromethylsulfanyl-phenyl)-urea (Ib)



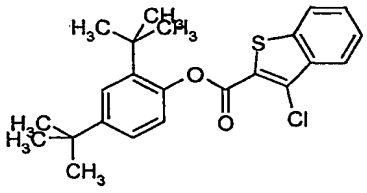
HAP1	4.2
EXO III	3.5
HPA II	< 20%

Oxa-[(2-chloro-4-tert-butyl)phenyl]-2-nitro-4-trifluoromethyl-phenol (Ia)



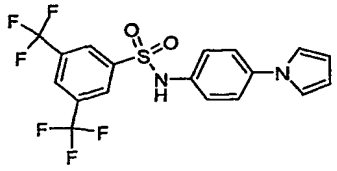
HAP1	11.8
EXO III	23
HPA II	< 20%

3-Chlorobenzo[b]thiophene-2-carboxylic acid 2,4-di-tert-butylphenyl ester (Ib)



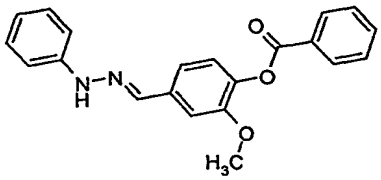
HAP1	0.8
EXO III	2.8
HPA II	< 20%

N-(4-Pyrrol-1-yl-phenyl)-3,5-bis-trifluoromethyl-benzenesulfonamide (Ia)



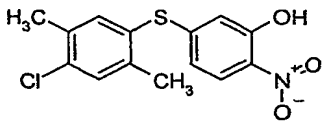
HAP1	19.6
EXO III	35.1
HPA II	< 20%

Benzoic acid 2-methoxy-4-(phenyl-hydrazonomethyl)-phenyl ester (Ia)



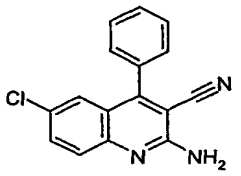
HAP1	46.2
EXO III	199.7
HPA II	< 20%

5-(4-Chloro-2,5-dimethyl-phenylsulfanyl)-2-nitro-phenol (Ia)



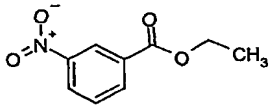
HAP1	26
EXO III	48.3
HPA II	< 20%

2-Amino-6-chloro-4-phenyl-quinoline-3-carbonitrile (Ib)



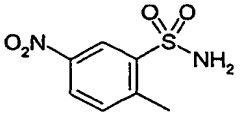
HAP1	31.1
EXO III	273.2
HPA II	< 20%

3-Nitro-benzoic acid ethyl ester (III)



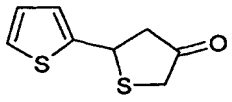
HAP1	63
EXO III	5.0
HPA II	< 20%

2-methyl-5-nitrobenzene-1-sulfonamide (III)



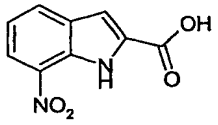
HAP1	3.6
EXO III	1.6
HPA II	< 20%

5-(2-thienyl)tetrahydrothiophen-3-one (V)



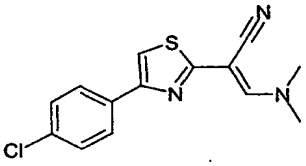
HAP1	12.8
EXO III	6.8
HPA II	< 20%

7-nitro-1H-indole-2-carboxylic acid (VI)



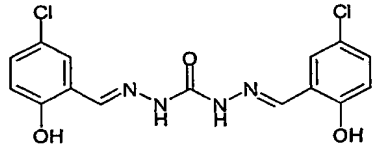
HAP1	3.5
EXO III	1.9
HPA II	< 20%

2-[4-(4-chlorophenyl)-1,3-thiazol-2-yl]-3-(dimethylamino)acrylonitrile (Ib)



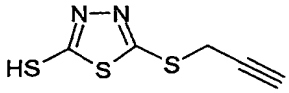
HAP1	3.4
EXO III	3.9
HPA II	< 20%

N'',N'''-di(5-chloro-2-hydroxybenzylidene)carbonic dihydrazide (Ia)



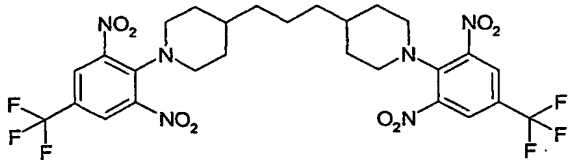
HAP1	>200
EXO III	3.0
HPA II	< 20%

5-(prop-2-ynylthio)-1,3,4-thiadiazole-2-thiol (V)



HAP1	3.4
EXO III	1.0
HPA II	< 20%

1-[2,6-dinitro-4-(trifluoromethyl)phenyl]-4-(3-{1-[2,6-dinitro-4-(trifluoro methyl)phenyl]-4-piperidyl}propyl)piperidine (Ia)



HAP1	>200
EXO III	19.8
HPA II	< 20%

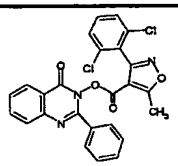
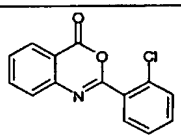
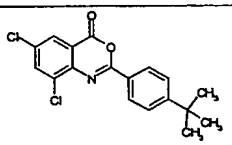
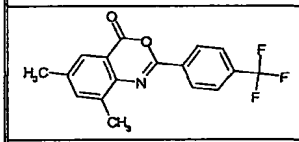
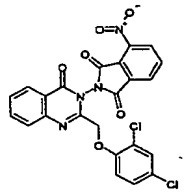
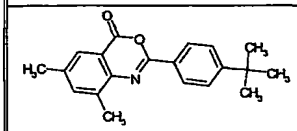
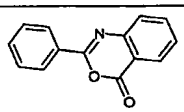
Table 2a

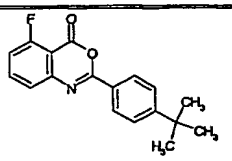
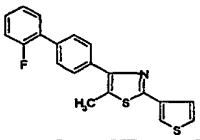
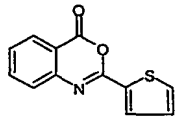
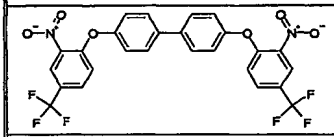
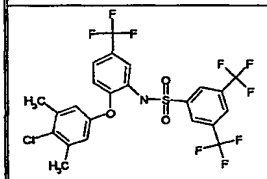
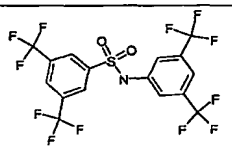
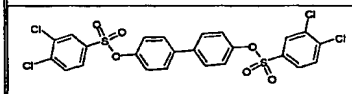
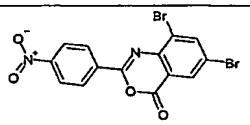
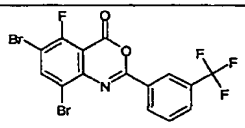
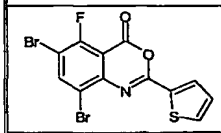
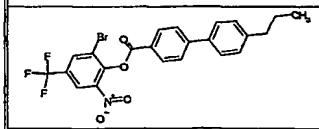
Key

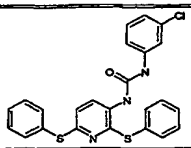
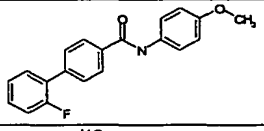
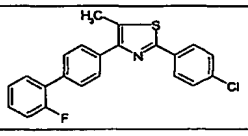
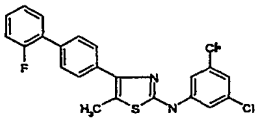
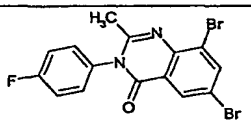
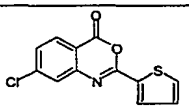
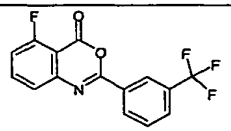
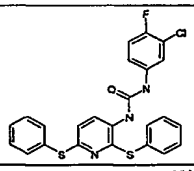
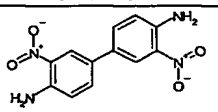
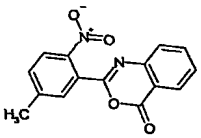
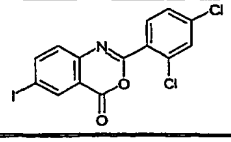
k_{20} = reaction rate in the presence of a 20 μM concentration of the selected inhibitor (expressed as a percentage of the reaction rate in the absence of inhibitor)

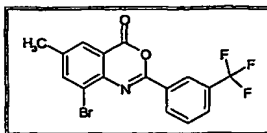
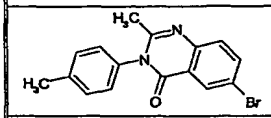
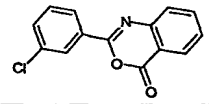
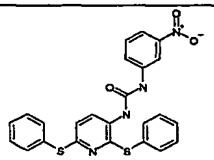
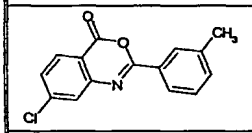
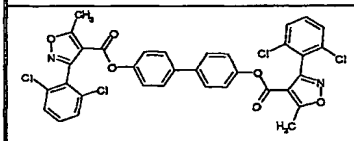
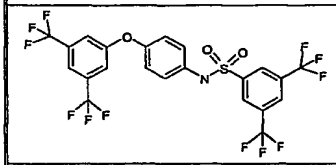
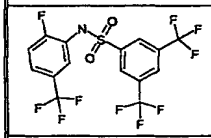
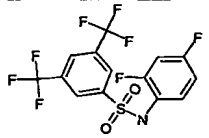
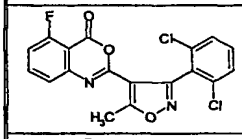
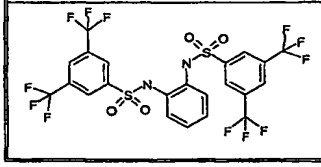
H = IC_{50} (in μM) vs. Hap1

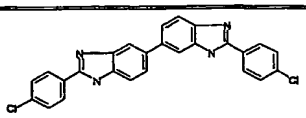
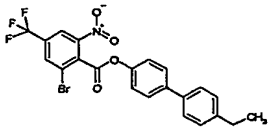
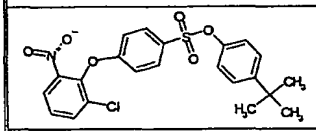
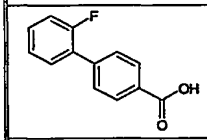
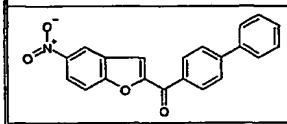
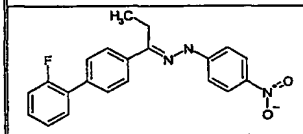
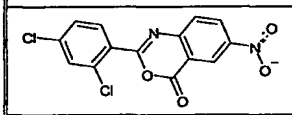
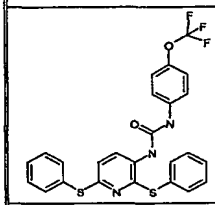
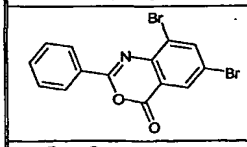
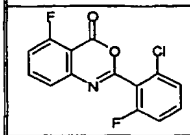
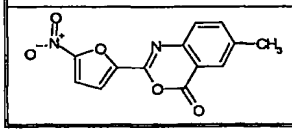
E = IC_{50} (in μM) vs. ExoIII

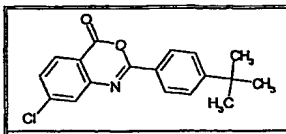
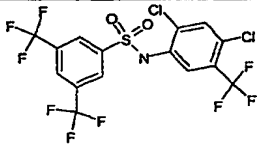
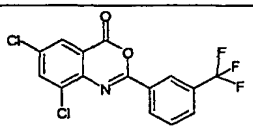
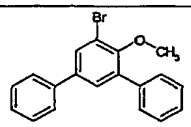
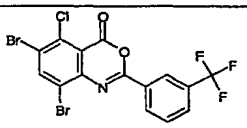
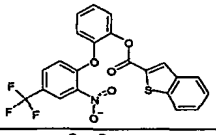
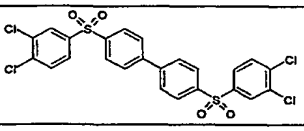
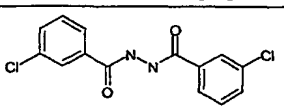
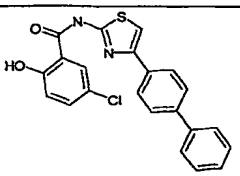
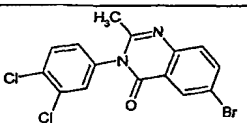
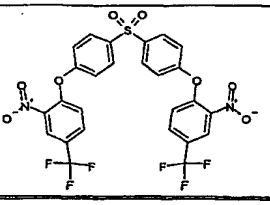
Compound	Name (formula)	k_{20}	H	E
	4-oxo-2-phenyl-3,4-dihydroquinazolin-3-yl 3-(2,6-dichlorophenyl)-5-methylisoxazole-4-carboxylate (Ib)	0	65.2	-
	2-(2-chlorophenyl)-4H-3,1-benzoxazin-4-one (IIa)	0	26.4	-
	2-[4-(tert-butyl)phenyl]-6,8-dichloro-4H-3,1-benzoxazin-4-one (IIa)	0	11.8	-
	6,8-dimethyl-2-[4-(trifluoromethyl)phenyl]-4H-3,1-benzoxazin-4-one (IIa)	0	17.7	-
	2-{2-[(2,4-dichlorophenoxy)-methyl]-4-oxo-3,4-dihydroquinazolin-3-yl}-4-nitroisoindoline-1,3-dione (IIa)	0	62.6	-
	2-[4-(tert-butyl)phenyl]-6,8-dimethyl-4H-3,1-benzoxazin-4-one (IIa)	0	14.3	-
	2-phenyl-4H-3,1-benzoxazin-4-one (IIa)	0	25.7	-

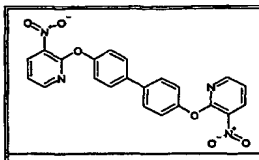
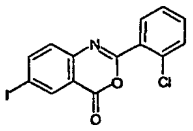
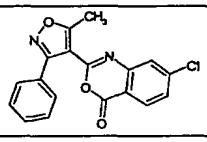
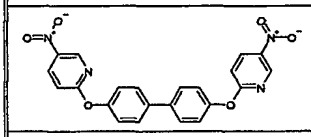
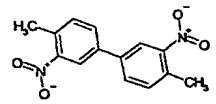
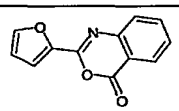
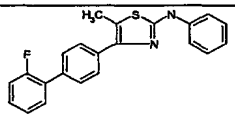
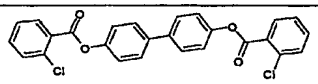
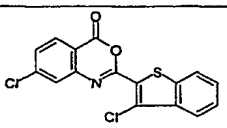
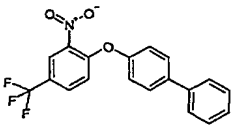
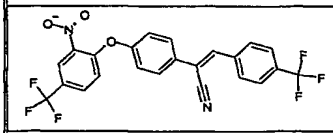
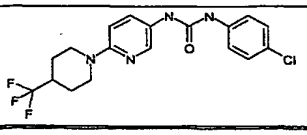
	2-[4-(tert-butyl)phenyl]-5-fluoro-4H-3,1-benzoxazin-4-one (IIa)	0	14.6	-
	4-(2'-fluoro[1,1'-biphenyl]-4-yl)-5-methyl-2-(3-thienyl)-1,3-thiazole (Ib)	0	3.7	-
	2-(2-thienyl)-4H-3,1-benzoxazin-4-one (IIa)	0	30	-
	4,4'-bis[2-nitro-4-(trifluoromethyl)phenoxy]-1,1'-biphenyl (Ia)	5	3	14.8
	N1-[2-(4-chloro-3,5-dimethylphenoxy)-5-(trifluoromethyl)phenyl]-3,5-di(trifluoromethyl)benzene-1-sulfonamide (Ia)	5	2.2	4.4
	N1-[3,5-di(trifluoromethyl)-phenyl]-3,5-di(trifluoromethyl)benzene-1-sulfonamide (Ia)	6	4.4	-
	4'-{[(3,4-dichlorophenyl)-sulfonyl]oxy}-[1,1'-biphenyl]-4-yl 3,4-dichlorobenzene-sulfonate (Ia)	7	1.8	-
	6,8-dibromo-2-(4-nitrophenyl)-4H-3,1-benzoxazin-4-one (IIa)	7	24.7	-
	6,8-dibromo-5-fluoro-2-[3-(trifluoromethyl)phenyl]-4H-3,1-benzoxazin-4-one (IIa)	7	88.7	-
	6,8-dibromo-5-fluoro-2-(2-thienyl)-4H-3,1-benzoxazin-4-one (IIa)	8	-	-
	2-bromo-6-nitro-4-(trifluoromethyl)phenyl 4'-propyl[1,1'-biphenyl]-4-carboxylate (Ia)	8	4	33.3

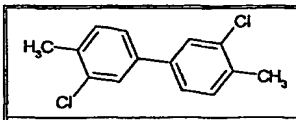
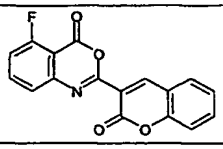
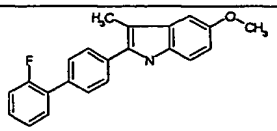
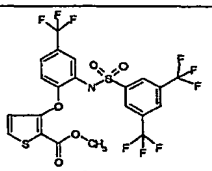
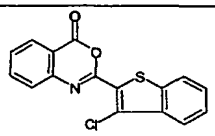
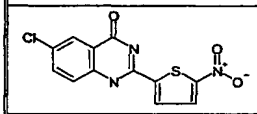
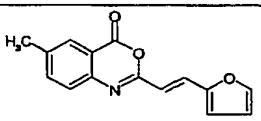
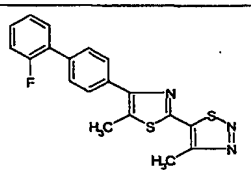
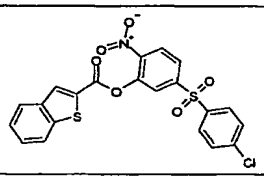
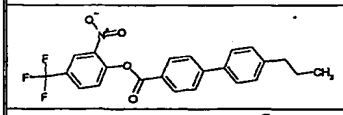
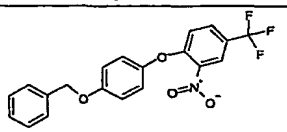
	N-[2,6-bis(phenylthio)-pyridin-3-yl]-N'-(3-chlorophenyl)urea (Ib)	8	3.2	10.5
	2'-fluoro-N-(4-methoxy-phenyl)[1,1'-biphenyl]-4-carboxamide (Ia)	8	11.5	-
	2-(4-chlorophenyl)-4-(2'-fluoro[1,1'-biphenyl]-4-yl)-5-methyl-1,3-thiazole (Ib)	9	1.3	55.1
	N-(3,5-dichlorophenyl)-4-(2'-fluoro[1,1'-biphenyl]-4-yl)-5-methyl-1,3-thiazol-2-amine (Ib)	9	0.9	-
	6,8-dibromo-3-(4-fluoro-phenyl)-2-methyl-3,4-di-hydroquinazolin-4-one (IIa)	9	-	-
	7-chloro-2-(2-thienyl)-4H-3,1-benzoxazin-4-one (IIa)	10	15.2	-
	5-fluoro-2-[3-(trifluoro-methyl)phenyl]-4H-3,1-benzoxazin-4-one (IIa)	10	23.7	-
	N-[2,6-bis(phenylthio)-pyridin-3-yl]-N'-(3-chloro-4-fluorophenyl)urea (Ib)	10	3.3	-
	3,3'-dinitro[1,1'-biphenyl]-4,4'-diamine (Ia)	10	15.8	-
	2-(5-methyl-2-nitrophenyl)-4H-3,1-benzoxazin-4-one (IIa)	11	49.5	-
	2-(2,4-dichlorophenyl)-6-iodo-4H-3,1-benzoxazin-4-one (IIa)	12	2.9	-

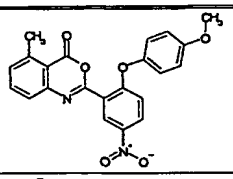
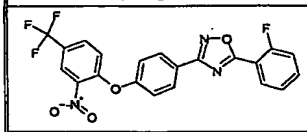
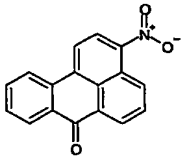
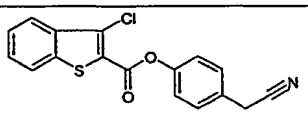
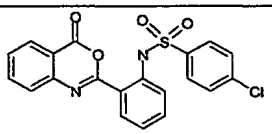
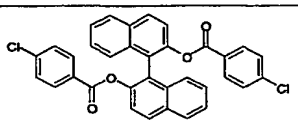
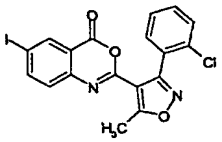
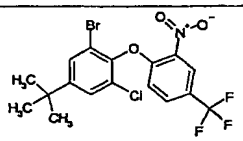
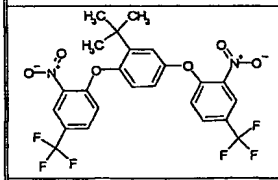
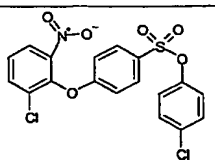
	8-bromo-6-methyl-2-[3-(trifluoromethyl)-phenyl]-4H-3,1-benzoxazin-4-one (IIa)	13	29.5 •	-
	6-bromo-2-methyl-3-(4-methylphenyl)-3,4-dihydro-quinazolin-4-one (IIa)	13	10.4	-
	2-(3-chlorophenyl)-4H-3,1-benzoxazin-4-one (IIa)	14	29.1	-
	N-[2,6-bis(phenylthio)-pyridin-3-yl]-N'-(3-nitrophenyl)urea (Ib)	14	9	-
	7-chloro-2-(3-methylphenyl)-4H-3,1-benzoxazin-4-one (IIa)	14	11.4	-
	4'-({[3-(2,6-dichlorophenyl)-5-methyl-isoxazol-4-yl]-carbonyl}oxy)[1,1'-biphenyl]-4-yl 3-(2,6-dichlorophenyl)-5-methylisoxazole-4-carboxylate (Ia)	15	-	-
	N1-{4-[3,5-di(trifluoro-methyl)phenoxy]-phenyl}-3,5-di(trifluoromethyl)-benzene-1-sulfonamide (Ia)	15	7.5	-
	N1-[2-fluoro-5-(trifluoro-methyl)phenyl]-3,5-di(trifluoromethyl)benzene-1-sulfonamide (Ia)	15	4.6	31.8
	N1-(2,4-difluorophenyl)-3,5-di(trifluoromethyl)benzene-1-sulfonamide (Ia)	16	5	-
	2-[3-(2,6-dichlorophenyl)-5-methylisoxazol-4-yl]-5-fluoro-4H-3,1-benzoxazin-4-one (Ib)	16	34.5	-
	N1-[2-({[3,5-di(trifluoro-methyl)phenyl]sulfonyl}-amino)phenyl]-3,5-di(trifluoromethyl)benzene-1-sulfonamide (Ia)	16	7.6	-

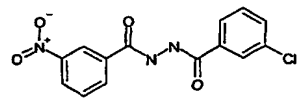
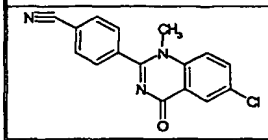
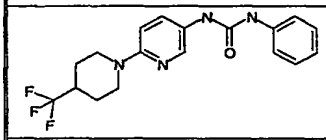
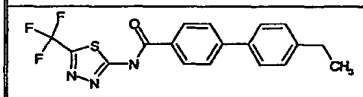
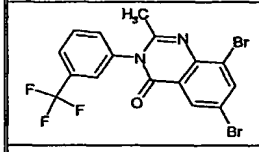
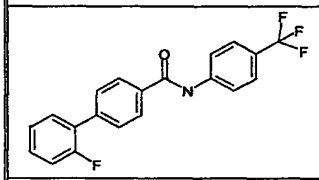
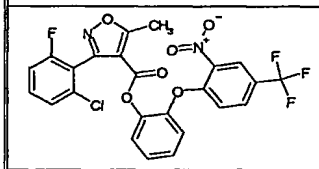
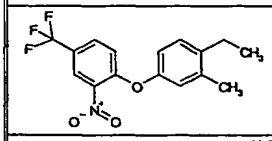
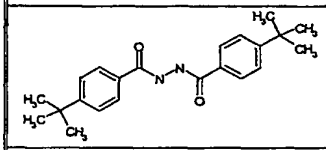
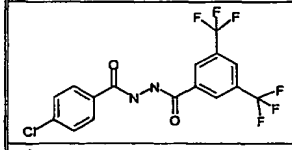
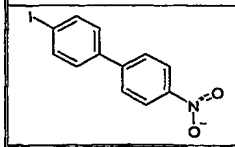
	2-(4-chlorophenyl)-5-[2-(4-chlorophenyl)-1H-benzo[d]-imidazol-6-yl]-1H-benzo[d]-imidazole (Ib)	16	4.2	-
	4'-ethyl[1,1'-biphenyl]-4-yl 2-bromo-6-nitro-4-(trifluoro-methyl)benzoate (Ia)	16	5.4	-
	4-(tert-butyl)phenyl 4-(2-chloro-6-nitro-phenoxy)-benzene-1-sulfonate (Ia)	17	1.7	-
	2'-fluoro[1,1'-biphenyl]-4-carboxylic acid (Ia)	17	7.4	-
	[1,1'-biphenyl]-4-yl(5-nitro-1-benzofuran-2-yl)methanone (Ib)	17	4.2	-
	1-(2'-fluoro[1,1'-biphenyl]-4-yl)propan-1-one N-(4-nitro-phenyl)hydrazone (Ia)	18	9.4	-
	2-(2,4-dichlorophenyl)-6-nitro-4H-3,1-benzoxazin-4-one (IIa)	18	2	-
	N-[2,6-bis(phenylthio)-pyridin-3-yl]-N'-[4-(trifluoro-methoxy)phenyl]urea (Ib)	19	4.1	12
	6,8-dibromo-2-phenyl-4H-3,1-benzoxazin-4-one (IIa)	20	31.7	-
	2-(2-chloro-6-fluorophenyl)-5-fluoro-4H-3,1-benzoxazin-4-one (IIa)	20	60.8	-
	6-methyl-2-(5-nitro-2-furyl)-4H-3,1-benzoxazin-4-one (IIa)	20	16.4	-

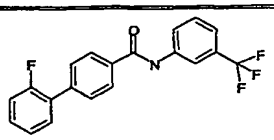
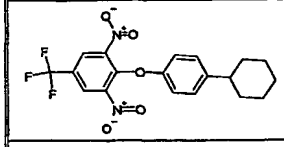
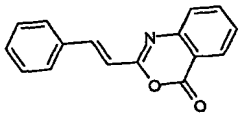
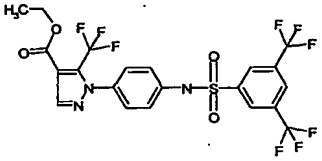
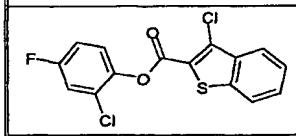
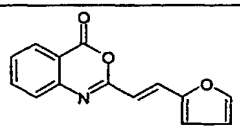
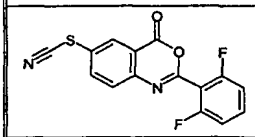
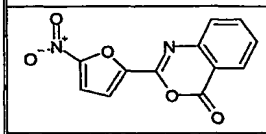
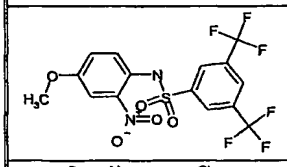
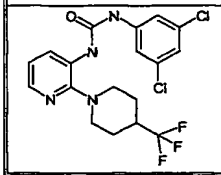
	2-[4-(tert-butyl)phenyl]-7-chloro-4H-3,1-benzoxazin-4-one (IIa)	21	4.3	244.9
	N1-[2,4-dichloro-5-(trifluoromethyl)phenyl]-3,5-di-(trifluoromethyl)benzene-1-sulfonamide (Ia)	21	6.1	-
	6,8-dichloro-2-[3-(trifluoromethyl)-phenyl]-4H-3,1-benzoxazin-4-one (IIa)	21	30.7	-
	3-bromo-2-methoxy-5-phenyl-1,1'-biphenyl (Ia)	21	8.5	-
	6,8-dibromo-5-chloro-2-[3-(trifluoromethyl)phenyl]-4H-3,1-benzoxazin-4-one (IIa)	22	21.2	-
	2-[2-nitro-4-(trifluoromethyl)phenoxy]phenyl benzo[b]thiophene-2-carboxylate (Ib)	22	16.2	-
	4,4'-bis[(3,4-dichlorophenyl)-sulfonyl]-1,1'-biphenyl (Ia)	22	13	-
	3-chloro-N'-(3-chloro-benzoyl)benzohydrazide (Ia)	22	-	-
	N-(4-[1,1'-biphenyl]-4-yl-1,3-thiazol-2-yl)-5-chloro-2-hydroxybenzamide (Ib)	23	8.3	35.2
	6-bromo-3-(3,4-dichloro-phenyl)-2-methyl-3,4-di-hydroquinazolin-4-one (IIa)	23	66.8	-
	2-nitro-1-[4-({4-[2-nitro-4-(trifluoromethyl)phenoxy]-phenyl}sulfonyl)phenoxy]-4-(trifluoromethyl)benzene (Ia)	23	15.2	-

	3-nitro-2-({4'-[(3-nitro-pyridin-2-yl)oxy]-[1,1'-biphenyl]-4-yl}oxy)pyridine (Ia)	24	13.6	-
	2-(2-chlorophenyl)-6-iodo-4H-3,1-benzoxazin-4-one (IIa)	24	6.6	36.2
	7-chloro-2-(5-methyl-3-phenylisoxazol-4-yl)-4H-3,1-benzoxazin-4-one (Ib)	25	2.2	13.8
	5-nitro-2-({4'-[(5-nitro-pyridin-2-yl)oxy]-[1,1'-biphenyl]-4-yl}oxy)pyridine (Ia)	26	23.6	-
	4,4'-dimethyl-3,3'-dinitro-1,1'-bipheny (Ia)l	26	4.4	-
	2-(2-furyl)-4H-3,1-benzoxazin-4-one (IIa)	27	-	-
	4-(2'-fluoro[1,1'-biphenyl]-4-yl)-5-methyl-N-phenyl-1,3-thiazol-2-amine (Ib)	27	-	-
	4'-[(2-chlorobenzoyl)oxy] [1,1'-biphenyl]-4-yl 2-chlorobenzoate (Ia)	27	-	-
	7-chloro-2-(3-chlorobenzo-[b]thiophen-2-yl)-4H-3,1-benzoxazin-4-one (IIa)	27	-	-
	4-[2-nitro-4-(trifluoro-methyl)phenoxy]-1,1'-biphenyl (Ia)	28	9	-
	2-{4-[2-nitro-4-(trifluoro-methyl)phenoxy]-phenyl}-3-[4-(trifluoromethyl)phenyl]-acrylonitrile (Ia)	28	8.5	-
	N-(4-chlorophenyl)-N'-{6-[4-(trifluoromethyl)piperidino]-3-pyridyl}urea (Ib)	29	-	-

	3,3'-dichloro-4,4'-dimethyl-1,1'-biphenyl (Ia)	30	-	-
	5-fluoro-2-(2-oxo-2H-chromen-3-yl)-4H-3,1-benzoxazin-4-one (IIa)	31	-	-
	2-(2'-fluoro[1,1'-biphenyl]-4-yl)-5-methoxy-3-methyl-1H-indole (Ib)	32	-	-
	methyl 3-[2-({[3,5-bis-(trifluoromethyl)phenyl]-sulfonyl}amino)-4-(trifluoro-methyl)phenoxy]thiophene-2-carboxylate (Ia)	32	40.4	-
	2-(3-chlorobenzo[b]thiophen-2-yl)-4H-3,1-benzoxazin-4-one (IIa)	32	-	-
	6-chloro-2-(5-nitro-2-thienyl)quinazolin-4(1H)-one (IIb)	32	-	-
	2-[2-(2-furyl)vinyl]-6-methyl-4H-3,1-benzoxazin-4-one (IIa)	32	6.5	-
	5-[4-(2'-fluoro[1,1'-biphenyl]-4-yl)-5-methyl-1,3-thiazol-2-yl]-4-methyl-1,2,3-thiadiazole (Ib)	33	-	-
	5-[(4-chlorophenyl)sulfonyl]-2-nitrophenyl benzo[b]-thiophene-2-carboxylate (Ib)	34	42.6	-
	2-nitro-4-(trifluoromethyl)-phenyl 4'-propyl[1,1'-biphenyl]-4-carboxylate (Ia)	34	13	-
	1-[4-(benzyloxy)phenoxy]-2-nitro-4-(trifluoromethyl)-benzene (Ia)	34	16.2	-

	2-[2-(4-methoxyphenoxy)-5-nitrophenyl]-5-methyl-4H-3,1-benzoxazin-4-one (Ia)	34	-	-
	5-(2-fluorophenyl)-3-{4-[2-nitro-4-(trifluoromethyl)-phenoxy]phenyl}-1,2,4-oxadiazole (Ib)	35	-	-
	3-nitro-7H-benzo[de]-anthracen-7-one (none)	36	-	-
	4-(cyanomethyl)phenyl 3-chlorobenzo[b]thiophene-2-carboxylate (Ib)	36	-	-
	N1-[2-(4-oxo-4H-3,1-benz-oxazin-2-yl)phenyl]-4-chloro-benzene-1-sulfonamide (Ia)	36	17.9	-
	1,1'-bis(4-chlorobenzoate) bi-2-naphthyl (IV)	36	-	-
	2-[3-(2-chlorophenyl)-5-methylisoxazol-4-yl]-6-iodo-4H-3,1-benzoxazin-4-one (Ib)	38	16.5	-
	1-bromo-5-(tert-butyl)-3-chloro-2-[2-nitro-4-(trifluoro-methyl)phenoxy]benzene (Ia)	38	-	-
	2-(tert-butyl)-1,4-di[2-nitro-4-(trifluoromethyl)phenoxy]-benzene (Ia)	38	-	-
	4-chlorophenyl 4-(2-chloro-6-nitro-phenoxy)benzene-1-sulfonate (Ia)	39	-	-

	N'1-(3-chlorobenzoyl)-3-nitrobenzene-1-carbo-hydrazide (Ia)	39	-	-
	4-(6-chloro-1-methyl-4-oxo-1,4-dihydroquinazolin-2-yl)benzonitrile (IIa)	39	-	-
	N-phenyl-N'-{6-[4-(trifluoro-methyl)piperidino]-3-pyridyl}urea (Ib)	40	-	-
	4'-ethyl-N-[5-(trifluorometh-yl)-1,3,4-thiadiazol-2-yl][1,1'-biphenyl]-4-carboxamide (Ib)	41	-	-
	6,8-dibromo-2-methyl-3-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-one (IIa)	41	-	-
	2'-fluoro-N-[4-(trifluoro-methyl)phenyl]-[1,1'-bi-phenyl]-4-carboxamide (Ia)	41	-	-
	2-[2-nitro-4-(trifluoro-methyl)phenoxy]-phenyl 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carboxylate (Ib)	41	-	-
	1-(4-ethyl-3-methylphenoxy)-2-nitro-4-(trifluoro-methyl)benzene (Ia)	41	-	-
	N'1-[4-(tert-butyl)benzoyl]-4-(tert-butyl)-benzene-1-carbohydrazide (Ia)	41	-	-
	N'1-(4-chlorobenzoyl)-3,5-di(trifluoromethyl)benzene-1-carbohydrazide (Ia)	42	-	-
	4-iodo-4'-nitro-1,1'-biphenyl (Ia)	43	-	-

	2'-fluoro-N-[3-(trifluoro-methyl)phenyl]-[1,1'-biphenyl]-4-carboxamide (Ia)	44	-	-
	2-(4-cyclohexylphenoxy)-1,3-dinitro-5-(trifluoromethyl)-benzene (Ia)	44	-	-
	2-styryl-4H-3,1-benzoxazin-4-one (IIa)	45	11.9	-
	ethyl 1-[4-({[3,5-di(trifluoro-methyl)-phenyl]sulfonyl}-amino)phenyl]-5-(trifluoro-methyl)-1H-pyrazole-4-carboxylate (Ia)	45	-	-
	2-chloro-4-fluorophenyl 3-chlorobenzo[b]thiophene-2-carboxylate (Ib)	45	-	-
	2-[2-(2-furyl)vinyl]-4H-3,1-benzoxazin-4-one (IIa)	46	12.3	-
	2-(2,6-difluorophenyl)-4-oxo-4H-3,1-benzoxazin-6-yl thiocyanate (IIa)	46	42.7	-
	2-(5-nitro-2-furyl)-4H-3,1-benzoxazin-4-one (IIa)	47	-	-
	N1-(4-methoxy-2-nitro-phenyl)-3,5-di(trifluoro-methyl)benzene-1-sulfonamide (Ia)	48	-	-
	N-(3,5-dichlorophenyl)-N'-{2-[4-(trifluoromethyl)-piperidino]-3-pyridyl}urea (Ib)	48	-	-

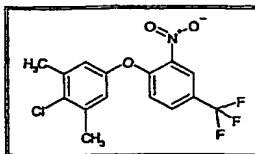
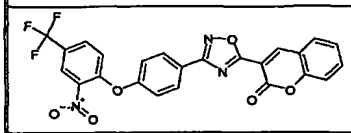
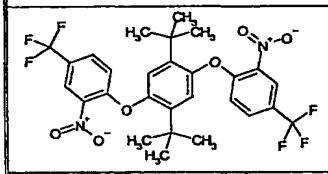
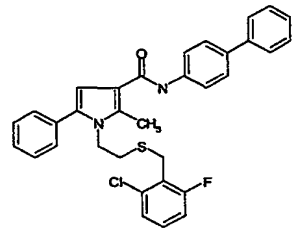
	2-chloro-1,3-dimethyl-5-[2-nitro-4-(trifluoromethyl)-phenoxy]benzene (Ia)	49	-	-
	3-(3-{4-[2-nitro-4-(trifluoro-methyl)-phenoxy]phenyl}-1,2,4-oxadiazol-5-yl)-2H-chromen-2-one (Ib)	49	-	-
	1,4-di(tert-butyl)-2,5-di[2-nitro-4-(trifluoromethyl)-phenoxy]benzene (Ia)	49	-	-
	N-[1,1'-biphenyl]-4-yl-1-{2-[(2-chloro-6-fluorobenzyl)-thio]ethyl}-2-methyl-5-phenyl-1H-pyrrole-3-carboxamide (Ib)	7	3.7	-

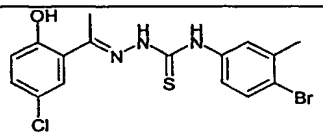
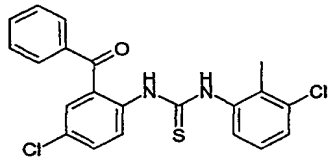
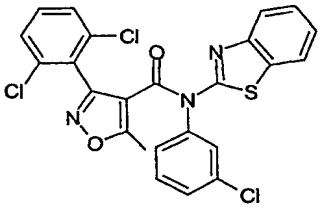
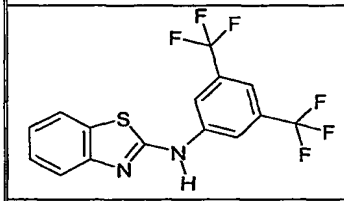
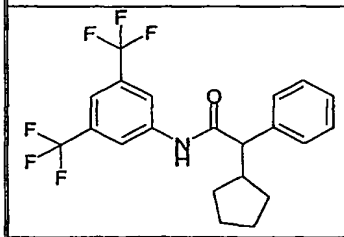
Table 2b

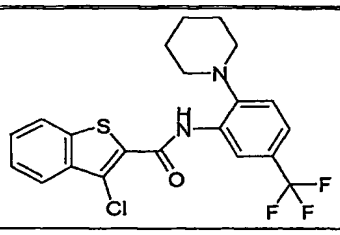
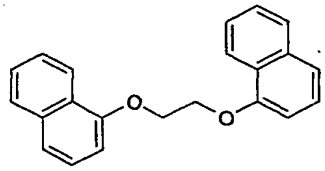
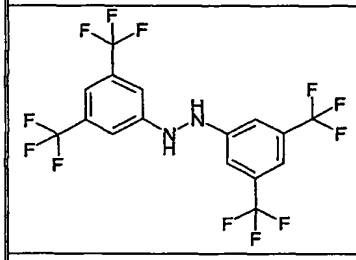
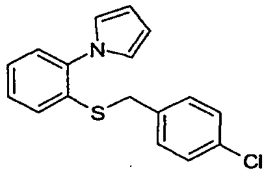
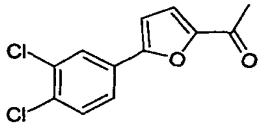
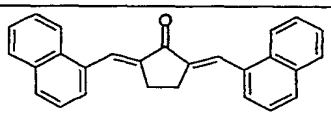
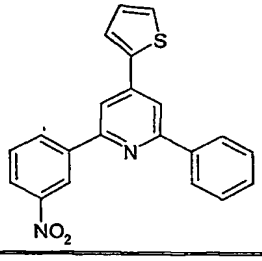
Key

k_5 = reaction rate in the presence of a 5 μM concentration of the selected inhibitor (expressed as a percentage of the reaction rate in the absence of inhibitor)

H = IC_{50} (in μM) vs. Hap1

E = IC_{50} (in μM) vs. ExoIII

Compound	Name (formula)	k_5	H	E
	N1-(4-bromo-3-methyl-phenyl)-2-[1-(5-chloro-2-hydroxyphenyl)-ethylidene]-hydrazine-1-carbothioamide (Ia)	5	-	-
	N-(2-benzoyl-4-chloro-phenyl)-N'-(3-chloro-2-methylphenyl)thiourea (Ia)	0	-	-
	N4-(1,3-benzothiazol-2-yl)-N4-(3-chlorophenyl)-3-(2,6-dichlorophenyl)-5-methyl-isoxazole-4-carboxamide (Ib)	0	-	-
	N2-[3,5-di(trifluoromethyl)-phenyl]-1,3-benzothiazol-2-amine (Ib)	3	-	-
	N1-[3,5-di(trifluoromethyl)-phenyl]-2-cyclopentyl-2-phenylacetamide (Ia)	7	-	-

	N2-[2-piperidino-5-(trifluoro-methyl)-phenyl]-3-chloro-benzo[b]thiophene-2-carboxamide (Ib)	0	-	-
	1-[2-(1-naphthyloxy)ethoxy]-naphthalene (IV)	6	-	-
	1,2-di[3,5-di(trifluoro-methyl)phenyl]-hydrazine (Ia)	6	-	-
	1-{2-[(4-chlorobenzyl)thio]-phenyl}-1H-pyrrole (Ib)	16	-	-
	1-[5-(3,4-dichlorophenyl)-2-furyl]ethan-1-one (Ib)	6	-	-
	2,5-di(1-naphthyl-methylidene)cyclo-pentan-1-one (IV)	1	4.4	3.7
	2-(3-nitrophenyl)-6-phenyl-4-(2-thienyl)-pyridine (Ib)	11	-	-

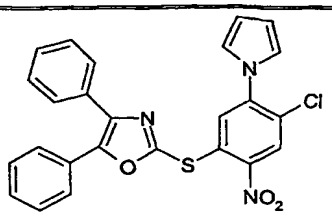
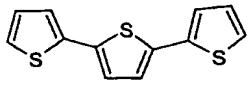
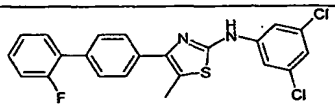
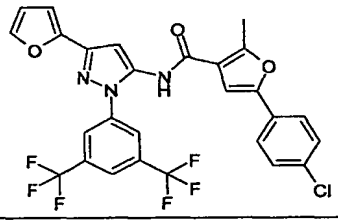
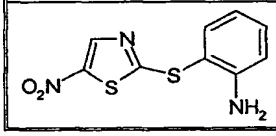
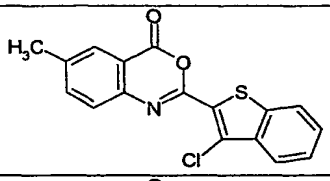
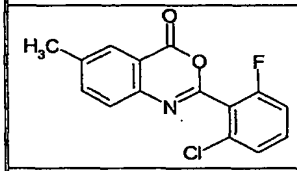
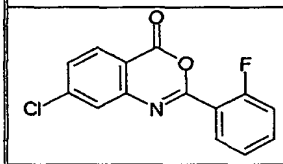
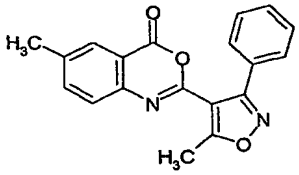
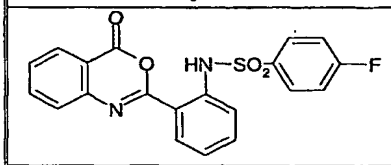
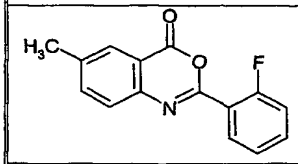
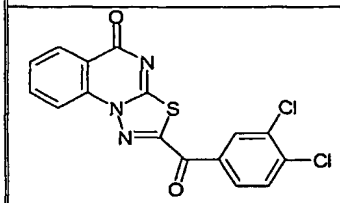
	2-{[4-chloro-2-nitro-5-(1H-pyrrol-1-yl)-phenyl]thio}-4,5-diphenyl-1,3-oxazole (Ib)	17	-	-
	2,5-bis(2-thienyl)thiophene (V)	15	-	-
	N-(3,5-dichlorophenyl)-4-(2'-fluoro[1,1'-biphenyl]-4-yl)-5-methyl-1,3-thiazol-2-amine (Ib)	16	0.9	-
	N-[1-[3,5-bis(trifluoro-methyl)phenyl]-3-(2-furyl)-1H-pyrazol-5-yl]-5-(4-chloro-phenyl)-2-methyl-3-furamide (Ib)	22	-	-
	2-[(5-nitro-1,3-thiazol-2-yl)thio]aniline (Ib)	43	-	-

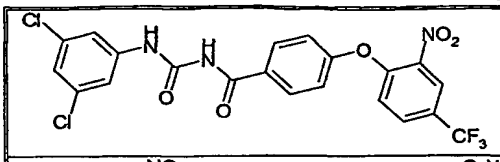
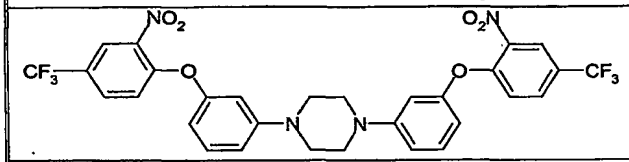
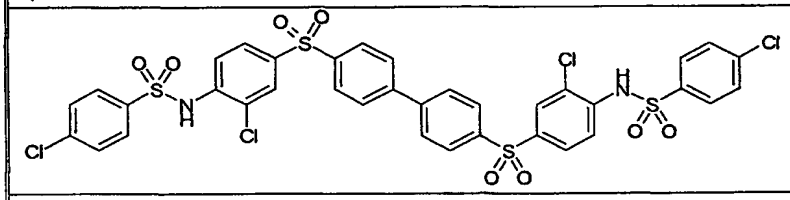
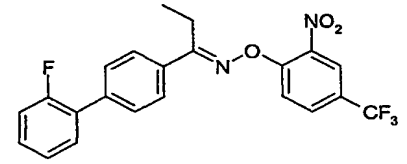
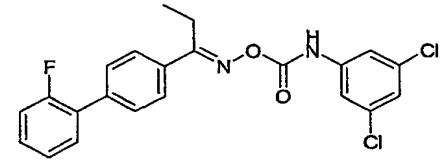
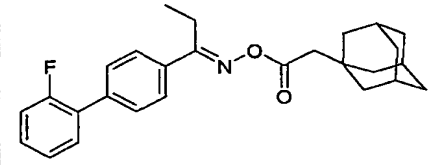
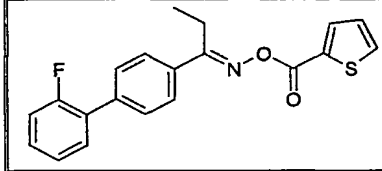
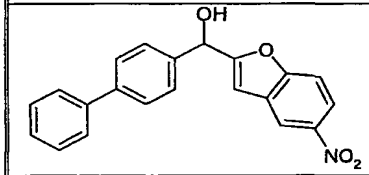
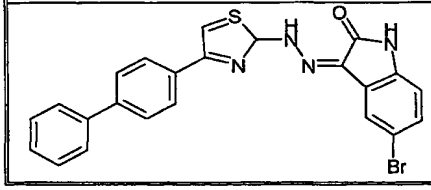
Table 2c

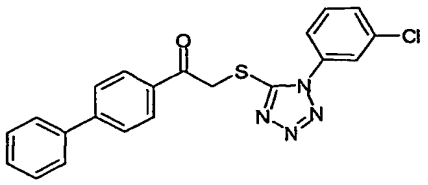
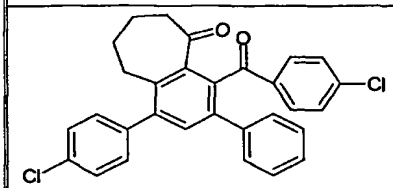
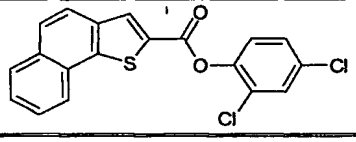
Key

H = IC_{50} (in μM) vs. Hap1

E = IC_{50} (in μM) vs. ExoIII

Compound	H	E
	10	-
	15	-
	1.6	30.1
	24.4	-
	25.8	-
	29	-
	10	-

	2.4	-
	13.9	-
	2.2	-
	2.4	-
	2.4	-
	2.7	-
	16.6	-
	9.2	-
	11.2	-

	10.4	-
	8.3	-
	2.9	-

Claims

1. The use of a low molecular weight mammalian AP endonuclease inhibitor, which inhibitor does not cleave AP sites in DNA, for the preparation of a medicament for the treatment of cancer.

2. Use as claimed in Claim 1, wherein the mammalian AP endonuclease inhibitor has a molecular weight of below 5000 g/mole.

3. Use as claimed in Claim 2, wherein the mammalian AP endonuclease inhibitor has a molecular weight of below 2500 g/mole.

4. Use as claimed in any one of the preceding claims wherein the mammalian AP endonuclease is an inhibitor of HAP1.

5. The use of a compound of formula I,

$$R^1—Ar^1—X—Ar^2—R^2 \qquad I$$

wherein Ar^1 represents aryl;

Ar^2 represents phenyl or Het^1;

Het^1 represents a wholly aromatic or part-aromatic five- to fourteen-membered heterocyclic group containing one or more heteroatoms selected from O, N and S;

R^1 and R^2 independently represent one or more optional substituents on Ar^1 and Ar^2, respectively, which substituents are selected from halo, nitro, cyano, OR^3, SR^4, $N(R^5)R^6$, aryl, Het^2, $C(O)R^7$, $C(R^{7a})=N\text{-}OR^{7b}$, $C(R^{7a})=N\text{-}N(H)R^{7b}$, $C(O)OR^8$, $C(O)N(R^9)R^{10}$, $S(O)_nR^{11}$ and $C_{1\text{-}12}$ alkyl (which latter group is optionally substituted and/or terminated by one or more substituents selected from halo, aryl, cyano and $N(R^{5a})R^{6a}$);

R^3 and R^4 independently represent H, C_{1-12} alkyl (optionally substituted and/or terminated by one or more substituents selected from halo and aryl), aryl, Het^3 or $C(O)R^{12a}$ or R^3 represents SO_2(aryl);

R^5 and R^6 independently represent H, C_{1-12} alkyl (optionally substituted and/or terminated by one or more substituents selected from halo and aryl), aryl, Het^4, $C(O)R^{12b}$, $C(O)N(R^{12c})R^{12d}$, $C(O)OR^{12d}$ or SO_2(aryl), or R^5 represents $N{=}C(R^{5b})(R^{6b})$;

R^{5a} and R^{6a} independently represent H or C_{1-6} alkyl;

R^{5b} and R^{6b} independently represent H or C_{1-6} alkyl, or R^{5b} and R^{6b}, together with the C-atom to which they are attached, form a 5- to 10-membered, monocyclic or bicyclic, fully saturated or partly aromatic, heterocyclic or carbocyclic ring system, wherein, when the ring system is heterocyclic, it contains one to three heteroatoms selected from O, N and S, and wherein the carbocyclic or heterocyclic ring system is optionally substituted by one or more substituents selected from halo, cyano, =O and C_{1-6} alkyl;

R^7 and R^8 independently represent H, C_{1-12} alkyl (optionally substituted and/or terminated by one or more substituents selected from halo and aryl), aryl or Het^5;

R^{7a} represents, at each occurrence, H or C_{1-6} alkyl;

R^{7b} represents, at each occurrence, C_{1-6} alkyl, aryl, Het^5, $C(O)R^{7c}$, $C(O)OR^{7d}$ or $C(O)N(R^{7e})R^{7f}$;

R^{7c} to R^{7f} independently represent C_{1-6} alkyl (optionally substituted by one or more substituents selected from halo, aryl and adamantyl), aryl or Het^5, or R^{7e} represents H;

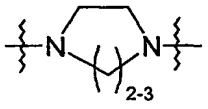
R^9 represents H, C_{1-12} alkyl (optionally substituted and/or terminated by one or more substituents selected from halo and aryl), aryl, Het^6 or $N(H)C(O)R^{12e}$;

R^{11} represents C_{1-12} alkyl (optionally substituted and/or terminated by one or more substituents selected from halo and aryl), aryl or Het^7;

n represents 1 or 2;

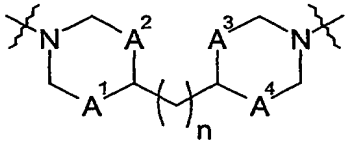
R^{10} and R^{12a} to R^{12e} independently represent H, C_{1-6} alkyl (optionally substituted and/or terminated by one or more substituents selected from halo and aryl), aryl or Het^8;

X represents a direct bond linking Ar^1 to Ar^2, the structural fragment



,

or the structural fragment



wherein the wavy lines indicates the bond positions of the fragment;
A^1 to A^4 independently represent a direct bond or CH_2; and
n represents 1 to 4;

or X represents the group A-D;
wherein A represents O, S, S(O), $S(O)_2$, $N(R^{13})$, C(O), CH(OH) or $C(R^{13a})$=; and

when A represents O, then D represents a direct bond, $S(O)_2$, $P(O)(OR^{14a})O$, C(O), C(S), C(O)O, $C(O)N(R^{15a})$ or $CH_2C(O)$;

when A represents S, then D represents a direct bond, C(O), C(S), C(O)O, $C(O)N(R^{15b})$, $CH_2C(O)NHNHC(S)NH$ or $CH_2C(O)$;

when A represents S(O) or $S(O)_2$, then D represents a direct bond or $CH_2C(O)$;

when A represents $N(R^{13})$, then D represents a direct bond, $N(R^{13b})$, $S(O)_2$, C(O), C(S), $C(O)C(R^{13c})(R^{13d})$, $C(O)N(R^{15c})$, $C(S)N(R^{15d})$, $C(S)N(H)N=C(R^{13e})$, $N=C(R^{14b})$- or $CH_2C(O)$;

when A represents C(O), then D represents a direct bond, $N(R^{15e})N(R^{15f})$, $N(R^{15g})N=C(R^{14c})$-, $N(R^{15h})N(R^{15i})C(O)$, $N(R^{15j})C(O)N(R^{15k})$ or $N(R^{16})C(R^{17})=N$-;

when A represents CH(OH), then D represents a direct bond;

when A represents $C(R^{13a})=$, then D represents $NN(H)C(O)N(H)N=C(R^{13f})$, N-O, N-OC(O), N-OC(O)O or $N\text{-}OC(O)N(R^{13g})$;

R^{13} represents H, C_{1-6} alkyl, aryl or Het^9;

R^{13a} to R^{13g} independently represent H or C_{1-6} alkyl;

R^{14a} to R^{14c} independently represent C_{1-6} alkyl or aryl, or R^{14b} and R^{14c} independently represent H;

R^{15a} to R^{15k} independently represent H, C_{1-6} alkyl, aryl or Het^{10};

R^{16} represents H, C_{1-6} alkyl, aryl or R^{16}, together with R^{17} and the N- and C-atoms to which those groups are attached, form a four- to seven-membered heterocyclic group containing at least one nitrogen atom (the atom to which R^{16} is attached) and optionally containing one or more further heteroatoms selected from O, N and S, which heterocyclic group is optionally unsaturated and/or substituted by one or more groups selected from OH, halo, cyano, nitro, C_{1-4} alkyl, C_{1-4} alkoxy, $=C(R^{18})R^{19}$ and *spiro*-$(CH_2)_p$;

R^{17} represents H, $C(R^{20a})(R^{20b})R^{20c}$, OR^{20d}, SR^{20e} or $N(R^{20f})R^{20g}$ or R^{17}, together with R^{16} and the N- and C-atoms to which those groups are attached, form a four- to seven-membered heterocyclic group containing at least one nitrogen atom (the atom to which R^{16} is attached) and optionally

containing one or more further heteroatoms selected from O, N or S, which heterocyclic group is optionally unsaturated and/or substituted by one or more groups selected from OH, halo, cyano, nitro, C_{1-4} alkyl, C_{1-4} alkoxy, $=C(R^{18})R^{19}$ and *spiro*-$(CH_2)_p$;

R^{18} and R^{19} independently represent H, C_{1-4} alkyl or aryl;

p represents 3 to 6;

R^{20a} to R^{20g} independently represent C_{1-6} alkyl, aryl or Het^{11} or R^{20a} to R^{20c} independently represent H;

Het^2 to Het^{11} independently represent, at each occurrence when used herein, four- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from O, N and S, which heterocyclic groups are optionally substituted by one or more substituents selected from =O, $-OR^{21a}$, $S(O)_qR^{21b}$, cyano, halo, nitro, C_{1-6} alkyl, aryl, $-N(R^{21c})R^{21d}$, $-C(O)R^{21e}$, $-C(O)OR^{21f}$, $-C(O)N(R^{21g})R^{21h}$, $-N(R^{21i})C(O)R^{21j}$, $-N(R^{21k})C(O)N(R^{21m})R^{21n}$ and $-N(R^{21o})S(O)_2R^{21p}$;

R^{21a} to R^{21p} independently represent H, C_{1-6} alkyl or aryl, provided that R^{21b} does not represent H when q represents 1 or 2; and

q represents 0, 1 or 2;

wherein each aryl or phenyl group, unless otherwise specified, is optionally substituted;

or a pharmaceutically acceptable derivative thereof;

for the preparation of a medicament for the treatment of cancer.

6. Use as claimed in Claim 5, wherein aryl is phenyl, or naphthyl, and wherein phenyl and naphthyl are optionally substituted by one or more substituents selected from $-OR^{21a}$, $S(O)_qR^{21b}$, cyano, halo, nitro, C_{1-6} alkyl, $-N(R^{21c})R^{21d}$, $-C(O)R^{21e}$, $-C(O)OR^{21f}$, $-C(O)N(R^{21g})R^{21h}$, $-N(R^{21i})C(O)R^{21j}$, $-N(R^{21k})C(O)N(R^{21m})R^{21n}$ and $-N(R^{21o})S(O)_2R^{21p}$, wherein R^{21a} to R^{21p}, p and q are as defined in Claim 5.

7. Use as claimed in Claim 5 or Claim 6, wherein alkyl and alkoxy groups are, where appropriate:

(a) straight-chain;

(b) branched-chain and/or cyclic; or

(c) part cyclic/acyclic.

8. Use as claimed in any one of Claims 5 to 7, wherein alkyl and alkoxy groups are, where appropriate:

(a) saturated or unsaturated;

(b) interrupted by one or more oxygen and/or sulfur atoms; and/or

(c) unless otherwise specified, substituted by one or more halo atoms.

9. Use as claimed in any one of Claims 5 to 8, wherein Ar^1 represents phenyl.

10. Use as claimed in Claim 9, wherein Het^1 represents a wholly aromatic or part-aromatic five- to twelve-membered heterocyclic group containing one to four heteroatoms selected from O, N and S.

11. Use as claimed in any one of Claims 5 to 10, wherein R^1 and R^2 independently represent one or more optional substituents on Ar^1 and Ar^2, respectively, which substituents are selected from halo, nitro, cyano, OR^3, SR^4, $N(R^5)R^6$, optionally substituted phenyl, Het^2, $C(O)R^7$, $C(O)OR^8$,

$C(O)N(R^9)R^{10}$, $S(O)_2$(optionally substituted phenyl) and C_{1-8} alkyl (which latter group is optionally unsaturated and/or substituted and/or terminated by one or more substituents selected from halo, cyano, $N(R^{5a})R^{6a}$ and optionally substituted phenyl).

12. Use as claimed in Claim 11, wherein R^3 and R^4 independently represent H, C_{1-8} alkyl (optionally substituted and/or terminated by one or more substituents selected from halo and phenyl, which latter group is optionally substituted), Het^3, optionally substituted phenyl or $C(O)R^{12a}$ or R^3 represents $S(O)_2$(optionally substituted phenyl).

13. Use as claimed in Claim 11 or Claim 12, wherein R^5 and R^6 independently represent H, C_{1-6} alkyl, optionally substituted phenyl, $C(O)R^{12b}$ or $S(O)_2$(optionally substituted phenyl).

14. Use as claimed in any one of Claims 11 to 13, wherein R^{5a} and R^{6a} independently represent H or C_{1-2} alkyl.

15. Use as claimed in any one of Claims 11 to 14, wherein R^7 and R^8 independently represent H, C_{1-6} alkyl, Het^5 or optionally substituted phenyl.

16. Use as claimed in any one of Claims 11 to 15, wherein R^9 represents H, C_{1-6} alkyl, optionally substituted phenyl, Het^6 or $N(H)C(O)R^{12e}$.

17. Use as claimed in any one of Claims 11 to 16, wherein R^{10}, R^{12a}, R^{12b} and R^{12e} independently represent H, C_{1-4} alkyl, optionally substituted phenyl or Het^8.

18. Use as claimed in any one of Claims 5 to 17, wherein A^1 to A^4 all represent CH_2.

19. Use as claimed in Claim 18, wherein n represents 3 or 4.

20. Use as claimed in any one of Claims 5 to 17, wherein when A represents O, then D represents a direct bond, $S(O)_2$, C(O) or C(O)N(H).

21. Use as claimed in any one of Claims 5 to 17, wherein when A represents S, then D represents a direct bond, C(O)N(H) or $CH_2C(O)NHNHC(S)NH$.

22. Use as claimed in any one of Claims 5 to 17, wherein when A represents $N(R^{13})$, then D represents a direct bond, N(H), $S(O)_2$, C(O), C(O)CH(*c*-pentyl), C(O)N(H), C(S)N(H), $C(S)N(H)N=C(CH_3)$ or $N=C(R^{14b})$-.

23. Use as claimed in any one of Claims 5 to 17, wherein when A represents C(O), then D represents a direct bond, N(H)N=C(H)-, N(H)N(H)C(O) or $N(R^{16})C(R^{17})=N$-.

24. Use as claimed in any one of Claims 5 to 17, wherein when A represents $C(R^{13a})=$, then D represents N-N(H)C(O)N(H)-N=C(H).

25. Use as claimed in Claim 22, wherein R^{13} represents H, C_{1-4} alkyl, optionally substituted phenyl or Het^9.

26. Use as claimed in Claim 24, wherein R^{13a} represents H or C_{1-2} alkyl.

27. Use as claimed in Claim 23, wherein R^{16} represents C_{1-4} alkyl or R^{16}, together with R^{17} and the N- and C-atoms to which those groups are attached, form a five-membered heterocyclic group containing at least one nitrogen atom (the atom to which R^{16} is attached) and optionally containing

one further heteroatom selected from O and S, which heterocyclic group is optionally substituted by one or more groups selected from C_{1-4} alkyl, $=C(R^{18})R^{19}$ and *spiro*-$(CH_2)_p$.

28. Use as claimed in Claim 23 or Claim 27, wherein R^{17} represents OR^{20d} or SR^{20e} or R^{17}, together with R^{16} and the N- and C-atoms to which those groups are attached, form a five-membered heterocyclic group containing at least one nitrogen atom (the atom to which R^{16} is attached) and optionally containing one further heteroatom selected from O and S, which heterocyclic group is optionally substituted by one or more groups selected from C_{1-4} alkyl, $=C(R^{18})R^{19}$ and *spiro*-$(CH_2)_p$.

29. Use as claimed in Claim 27 or Claim 28, wherein R^{18} and R^{19} independently represent H or C_{1-2} alkyl.

30 Use as claimed in any one of Claims 27 to 29, wherein p represents 4 or 5.

31. Use as claimed in any one of Claims 27 to 30, wherein R^{20d} and R^{20e} independently represent C_{1-4} alkyl or optionally substituted phenyl.

32. Use as claimed in any one of Claims 5 to 31, wherein Het^2 represents a four- to seven-membered monocyclic heterocyclic group or a nine- to eleven-membered bicyclic heterocyclic group, which heterocyclic group contains one to four heteroatoms selected from O, N and S, and which heterocyclic group is optionally substituted by one or more substituents selected from =O, cyano, halo, phenyl (which latter group is optionally substituted), C_{1-6} alkyl, $-N(R^{21c})R^{21d}$, $-C(O)R^{21e}$ and $C(O)OR^{21f}$.

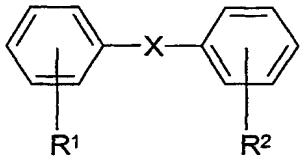
33. Use as claimed in any one of Claims 5 to 32, wherein Het^5, Het^6 and Het^9 independently represent six- to ten-membered heterocyclic groups containing one to four heteroatoms selected from O, N and S, which heterocyclic groups are optionally substituted by one or more substituents selected from =O, cyano, halo, C_{1-6} alkyl and optionally substituted phenyl.

34. Use as claimed in any one of Claims 5 to 33, wherein Het^3 and Het^8 independently represent four to seven-membered heterocyclic groups containing one to four heteroatoms selected from O, N and S, which heterocyclic groups are optionally substituted by one or more substituents selected from cyano, halo, nitro, C_{1-6} alkyl, optionally substituted phenyl and $C(O)OR^{21f}$.

35. Use as claimed in any one of Claims 5 to 34, wherein optional substituents on phenyl groups are one or more substituents selected from $-OR^{21a}$, SR^{21b}, cyano, halo, nitro, C_{1-6} alkyl and $-NH_2$.

36. Use as claimed in any one of Claims 5 to 35, wherein R^{21a} to R^{21f} independently represent H or C_{1-4} alkyl.

37. Use as claimed in Claim 5, which comprises the use of a compound of formula Ia,



Ia

wherein R^1 and R^2 independently represent one or more optional substituents selected from halo, nitro, C_{1-8} alkyl (which latter group is optionally unsaturated and/or substituted and/or terminated by (i) one or more halo atoms, or (ii) by cyano and phenyl (which latter group is optionally substituted by C_{1-2} alkyl)), OR^3, $N(H)R^6$, phenyl (which latter

group is optionally substituted by one or more halo atoms) Het^2, $C(O)R^7$, $C(O)OR^8$, $S(O)_2$(phenyl) (the phenyl part of which latter group is optionally substituted by one or two halo atoms) and $C(O)N(H)N(H)C(O)R^{12e}$;

R^3 represents H, C_{1-4} alkyl (optionally substituted by phenyl), phenyl (which latter group is optionally substituted by one or more substituents selected from halo, nitro and C_{1-4} alkyl), Het^3, $C(O)R^{12a}$ or $S(O)_2$(phenyl) (the phenyl part of which latter group is optionally substituted by one or two halo atoms);

R^6 represents H or $S(O)_2$(phenyl) (the phenyl part of which latter group is optionally substituted by one or two C_{1-2} alkyl groups);

R^7 represents phenyl optionally substituted by one to three halo atoms;

R^8 represents H or phenyl (which latter group is optionally substituted by one to three substituents selected from halo, nitro and C_{1-2} alkyl);

R^{12a} represents phenyl (optionally substituted by one to three substituents selected from halo, nitro and C_{1-2} alkyl) or Het^8;

R^{12e} represents phenyl (optionally substituted by one or more substituents selected from halo and C_{1-4} alkyl);

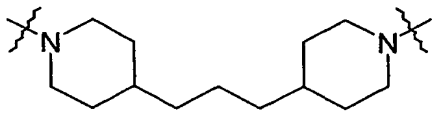
Het^2 represents a five-membered aromatic heterocyclic group containing one or two heteroatoms selected from O, N and S, which heterocyclic group is optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl and $C(O)O(C_{1-2}$ alkyl) or Het^2 represents a partly aromatic ten-membered bicyclic heterocyclic group containing one or two heteroatoms selected from N and O, which heterocyclic group is optionally substituted by one or more substituents selected from =O and C_{1-2} alkyl;

Het^3 represents an aromatic five- or six-membered heterocyclic group containing one heteroatom selected from N and S and optionally containing one or two further N-atoms, which heterocyclic group is optionally substituted by nitro or $C(O)O(C_{1-2}$ alkyl);

Het^8 represents an aromatic five-membered heterocyclic group containing one heteroatom selected from N, O and S and optionally containing one or

two further N-atoms, which heterocyclic group is optionally substituted by one to three substituents selected from C_{1-2} alkyl and phenyl (which latter group is optionally substituted by one or two halo atoms);

X represents a direct bond, O, S, $S(O)_2$, $SCH_2C(O)NHNHC(S)NH$, $OS(O)_2$, $N(H)N(H)$, $N(H)S(O)_2$, $N(H)N=C(R^{14b})$-, $N(R^{13})C(O)$, $N(H)C(O)CH(c$-pentyl), $N(H)C(S)N(H)$, $N(H)C(S)N(H)N=C(CH_3)$-, $C(O)N(H)N=CH$-, $C(O)N(H)N(H)C(O)$, -CH=NN(H)C(O)N(H)N=CH- or the structural fragment



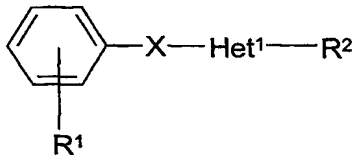
;

R^{13} represents H, phenyl (which latter group is optionally substituted by one or more substituents selected from halo and C_{1-4} alkyl) or Het^9;

R^{14b} represents H or ethyl;

Het^9 represents a nine-membered bicyclic aromatic heterocyclic group containing one or two heteroatoms selected from O, N and S, which heterocyclic group is optionally substituted by one or more halo or C_{1-4} alkyl groups.

38. Use as claimed in Claim 5, which comprises the use of a compound of formula Ib,



Ib

wherein Het^1 represents a wholly aromatic five- or six-membered monocyclic heterocyclic group containing one N-, O- or S-atom and optionally containing one or more further N-atoms or Het^1 represents a nine- to eleven-membered wholly aromatic or part-aromatic bicyclic heterocyclic group containing one or two heteroatoms selected from O, N and S;

R^1 and R^2 represent one or more optional substituents on the phenyl group and Het^1, respectively, which substituents are selected from halo, nitro, cyano, OR^3, SR^4, $N(R^5)(R^6)$, phenyl (which latter group is optionally substituted by one or more substituents selected from halo and C_{1-2} alkyl), Het^2, $C(O)R^7$, $C(O)OHet^5$, $C(O)N(R^9)(R^{10})$, $S(O)_2$(phenyl) (the phenyl part of which latter group is optionally substituted by one or two chloro atoms) and C_{1-8} alkyl (which latter group is (i) optionally substituted and/or terminated by cyano or one or more halo atoms, (ii) unsaturated and substituted and/or terminated by cyano and $N(CH_3)_2$, or (iii) interrupted by S and substituted or terminated by phenyl (which latter group is optionally substituted by one or more halo atoms));

R^3 represents H, C_{1-4} alkyl (which latter group is optionally substituted by one or more halo atoms) or phenyl (which latter group is optionally substituted by one to three substituents selected from halo, nitro and C_{1-2} alkyl);

R^4 represents C_{1-4} alkyl (optionally substituted and/or terminated by one or more fluoro atoms or by phenyl, which latter group is optionally substituted by one to three halo atoms) or phenyl (which latter group is optionally substituted by one or more substituents selected from halo and C_{1-4} alkyl);

R^5 and R^6 both represent H or R^5 represents H and R^6 represents phenyl (which latter group is optionally substituted by one to three halo atoms) or $C(O)R^{12b}$;

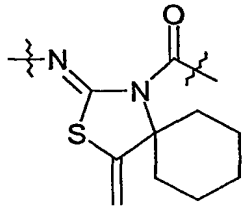
R^7 represents C_{1-2} alkyl;

R^9 represents Het^6;

R^{10} represents H or phenyl, which latter group is optionally substituted by one to three halo atoms;

R^{12b} represents phenyl (optionally substituted by one or two substituents selected from OH and halo) or Het^8;

X represents a direct bond, S, C(O), N(H), N(H)C(O), OC(O) (wherein, in which latter two groups, the C(O) group is attached either to Het^1 or to the phenyl group that bears R^1), N(H)C(O)N(H) or the structural fragment



,

wherein the wavy lines represent the points of attachment to the rest of the molecule and wherein the C(O) group is attached to Het^1;

Het^2 represents a wholly aromatic five-membered heterocyclic group containing one to three heteroatoms selected from O, N and S, which heterocyclic group is optionally substituted by methyl, Het^2 represents a fully saturated six-membered heterocyclic group containing one or two N-atoms, which heterocyclic group is optionally substituted by trifluoromethyl, or Het^2 represents a wholly or partly aromatic nine- or ten-membered heterocyclic group containing one or two heteroatoms selected from N and O, which heterocyclic group is optionally substituted by one to three substituents selected from =O, halo and phenyl (which latter group is optionally substituted by halo);

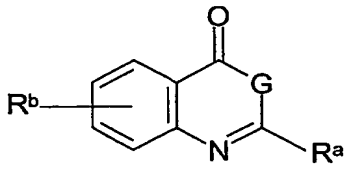
Het^5 represents a nine- or ten-membered heterocyclic group containing one or two heteroatoms selected from N and O, which heterocyclic group is optionally substituted by one to three substituents selected from =O, halo and phenyl;

Het^6 represents a nine-membered bicyclic aromatic heterocyclic group containing one or two heteroatoms selected from O, N and S;

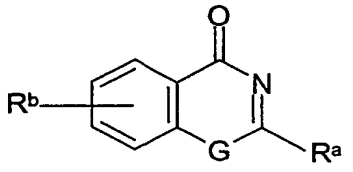
Het^8 represents a five-membered heterocyclic group containing one heteroatom selected from O, N and S, which heterocyclic group is optionally substituted by one or two substituents selected from methyl and

phenyl (which latter group is optionally substituted by one or two halo atoms).

39. The use of a compound of formula IIa or IIb,



IIa



IIb

wherein

R^a represents aryl, Het^a or C_{1-12} alkyl, which latter group is optionally substituted and/or terminated by one or more substituents selected from halo, OR^c, aryl and Het^b, or R^a, together with R^d and the C- and N-atoms to which they are attached, form a 5- or 6-membered heterocyclic ring containing one N-atom (the atom to which R^d is attached) and optionally containing one or more further heteroatoms selected from N, O and S, which heterocyclic ring is fully saturated, partially unsaturated or aromatic in character and is optionally substituted by one or more substituents selected from =O, OH, halo, nitro, cyano, C_{1-6} alkyl, aryl, NH_2 and $C(O)R^{d1}$;

R^c represents H, C_{1-6} alkyl or aryl;

R^{d1} represents H, C_{1-6} alkyl or aryl;

R^b represents one or more optional substituents selected from halo, nitro, cyano, -SCN, C_{1-6} alkyl and NH_2;

G represents O or $N(R^d)$;

R^d represents H, C_{1-12} alkyl, aryl, Het^c or R^d, together with R^a and the N- and C-atoms to which they are attached, form a 5- or 6-membered heterocyclic ring containing one N-atom (the atom to which R^d is attached) and optionally containing one or more further heteroatoms selected from N,

O and S, which heterocyclic ring is fully saturated, partially unsaturated or aromatic in character and is optionally substituted by one or more substituents selected from =O, OH, halo, nitro, cyano, C_{1-6} alkyl, aryl, NH_2 and $C(O)R^{dl}$; and

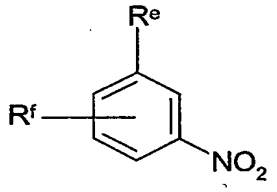
Het^a, Het^b and Het^c independently represent four- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from N, O and S, which heterocyclic groups are optionally substituted by one or more substituents selected from =O, OH, halo, nitro, cyano, C_{1-6} alkyl, aryl and NH_2;

wherein each aryl group, unless otherwise specified, is optionally substituted;

or a pharmaceutically acceptable derivative thereof;

for the preparation of a medicament for the treatment of cancer.

40. The use of a compound of formula III,



III

wherein R^e represents $C(O)OR^g$, $C(O)N(R^h)(R^i)$ or $S(O)_2N(R^h)(R^i)$;

R^f represents one or more optional substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy and halo;

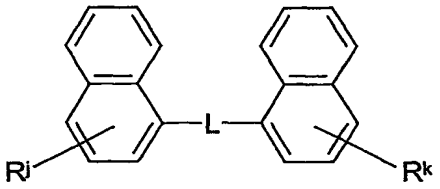
R^g represents C_{1-6} alkyl; and

R^h and R^i independently represent, at each occurrence when used herein, H or C_{1-6} alkyl;

or a pharmaceutically acceptable derivative thereof;

for the preparation of a medicament for the treatment of cancer.

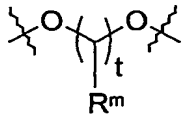
41. The use of a compound of formula IV,



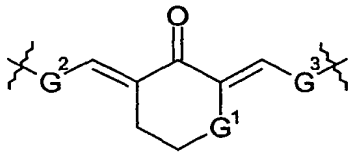
IV

wherein R^j and R^k independently represent one or more optional substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, nitro, cyano, halo and OC(O)aryl;

L represents a direct bond or a structural fragment of formula IVa or IVb,



IVa



IVb

wherein t represents 2, 3 or 4;

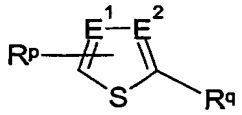
R^m represents, independently at each occurrence, H or C_{1-3} alkyl; and

G^1, G^2 and G^3 independently represent a direct bond or $(CH_2)_{1-2}$;

or a pharmaceutically acceptable derivative thereof;

for the preparation of a medicament for the treatment of cancer.

42. The use of a compound of formula V,



V

wherein E^1 and E^2 independently represent CH or N;

R^p represents one to three optional substituents selected from C_{1-4} alkyl, halo, cyano, nitro, OH and SH;

R^q represents Het^x or SR^r;

Het^x represents a wholly aromatic or fully saturated five-membered heterocycle containing one or more heteroatoms selected from N, O and S, which heterocyclic group is optionally substituted by one or more substituents selected from C_{1-4} alkyl, halo, cyano, nitro, OH, =O and thienyl;

R^r represents C_{1-6} alkyl;

or a pharmaceutically acceptable derivative thereof;

for the preparation of a medicament for the treatment of cancer.

43. Use as claimed in any one of Claims 39 to 42, wherein aryl is phenyl, or naphthyl, which latter two groups are optionally substituted by one or more substituents selected from $-OR^{21a}$, $S(O)_qR^{21b}$, cyano, halo, nitro, C_{1-6} alkyl, $-N(R^{21c})R^{21d}$, $-C(O)R^{21e}$, $-C(O)OR^{21f}$, $-C(O)N(R^{21g})R^{21h}$, $-N(R^{21i})C(O)R^{21j}$, $-N(R^{21k})C(O)N(R^{21m})R^{21n}$ and $-N(R^{21o})S(O)_2R^{21p}$, wherein R^{21a} to R^{21p}, p and q are as defined in Claim 5.

44. Use as claimed in any one of Claims 39 to 43, wherein alkyl groups are, where appropriate:

(a) straight-chain;

(b) branched-chain and/or cyclic; or

(c) part cyclic/acyclic.

45. Use as claimed in any one of Claims 39 to 44, wherein alkyl groups are, where appropriate:

(a) saturated or unsaturated;

(b) interrupted by one or more oxygen and/or sulfur atoms; and/or

(c) unless otherwise specified, substituted by one or more halo atoms.

46. Use as claimed in any one of Claims 39 and 43 to 45, wherein R^a represents Het^a or optionally unsaturated and/or branched C_{1-6} alkyl.

47. Use as claimed in any one of Claims 39 and 43 to 46, wherein R^b represents one or more optional substituents selected from halo and C_{1-4} alkyl.

48. Use as claimed in any one of Claims 39 and 43 to 47, wherein R^c represents H, C_{1-4} alkyl or phenyl (which latter group is optionally substituted by one or more substituents selected from halo and C_{1-4} alkyl).

49. Use as claimed in any one of Claims 39 and 43 to 48, wherein Het^a represents an aromatic five- to ten-membered heterocyclic group containing one or two heteroatoms selected from N, O and S, which heterocyclic group is optionally substituted by one to three substituents selected from halo, cyano and C_{1-4} alkyl.

50. The use of a low molecular weight HAP1 inhibitor selected from the following group:

(i) 3,5,3',5'-Tetra-tert-butyl-biphenyl-4,4'-diol;

(ii) 3,4,5,3',4',5'-Hexabromo-biphenyl;

(iii) 4'-Bromo-4-pentyl-biphenyl;

(iv) 4,4'-Bis-(2-chloro-6-nitro-phenoxy)-biphenyl;

(v) 4-Hexyl-biphenyl;

(vi) Oxa-[(4-chloro-2-cyclohexyl)phenyl]-2-nitro-4-trifluoromethyl-phenol;

(vii) Oxa-[(2-chloro-4-tert-butyl)phenyl]-2-nitro-4-trifluoromethyl-phenol;

(viii) 5-(4-Chloro-2,5-dimethyl-phenylsulfanyl)-2-nitro-phenol;

(ix) 3,5-Dichloro-benzenesulfonic acid 2-bromo-4-tert-butyl-6-chloro-phenyl ester;

(x) 1-(2,6-Dibromo-4-cyclohexyl-phenyl)-1H-pyrrole;

(xi) 5-(3,4-Dichloro-phenyl)-2H-tetrazole;

(xii) N-(4-Pyrrol-1-yl-phenyl)-3,5-bis-trifluoromethyl-benzene-sulfonamide;

(xiii) 2-Amino-6-chloro-4-phenyl-quinoline-3-carbonitrile;

(xiv) 3-(4-Fluoro-phenyl)-3,7,8-trimethyl-1,5-dihydro-benzo[e][1,3]-dithiepine;

(xv) 4-tert-Butyl-benzoic acid (3,5-dichloro-2-hydroxy-benzylidene)-hydrazide;

(xvi) 3-Chloro-benzo[b]thiophene-2-carboxylic acid 2,4-di-tert-butyl-phenyl ester;

(xvii) (3-Chloro-benzo[b]thiophen-2-yl)-[2-(2-chloro-phenylimino)-4-methylene-3-thia-1-aza-spiro[4.5]dec-1-yl]-methanone;

(xviii) Benzoic acid 2-methoxy-4-(phenyl-hydrazonomethyl)-phenyl ester;

(xix) 6,8-Dibromo-2-(1-methyl-propenyl)-benzo[d][1,3]oxazin-4-one;

(xx) N-Benzothiazol-2-yl-N-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-benzamide;

(xxi) (5,7-Dichloro-benzofuran-2-yl)-(4-trifluoromethoxy-phenyl)-methanone;

(xxii) 2-(4-Bromo-thiophen-2-yl)-6-chloro-1H-quinazolin-4-one;

(xxiii) 1-[6-(4-Chloro-phenylsulfanyl)-pyridin-3-yl]-3-(4-trifluoromethyl-sulfanyl-phenyl)-urea;

(xxiv) 3,5-Didodecyl-[1,3,5]thiadiazinane-2-thione;

(xxv) 6,8-Dibromo-3-(3,4-dichloro-phenyl)-2-methyl-3H-quinazolin-4-one;

(xxvi) N-[(4-tert-butyl-benzoyl)-amino]-3-tert-Butyl-5-[N'-(4-tert-butyl-benzoyl)-hydrazinocarbonyl]-benzamide;

(xxvii) 2,5-Dimethoxy-4-nitro-thia-(N'[N-(2-chloro-5-trifluoromethyl)-phenyl)thiocarboxyamino]hyrazinecarbonylmethyl]phenol;

(xxviii) 3-Nitro-benzoic acid ethyl ester;

(xxix) N1-(4-bromo-3-methylphenyl)-2-[1-(5-chloro-2-hydroxyphenyl)-ethylidene]hydrazine-1-carbothioamide;

(xxx) 2-Methyl-5-nitrobenzene-1-sulfonamide;

(xxxi) N-(2-Benzoyl-4-chlorophenyl)-N'-(3-chloro-2-methylphenyl)-thiourea;

(xxxii) N4-(1,3-Benzothiazol-2-yl)-N4-(3-chlorophenyl)-3-(2,6-dichloro-phenyl)-5-methylisoxazole-4-carboxamide;

(xxxiii) N2-[3,5-Di(trifluoromethyl)phenyl]-1,3-benzothiazol-2-amine;

(xxxiv) N1-[3,5-Di(trifluoromethyl)phenyl]-2-cyclopentyl-2-phenyl-acetamide;

(xxxv) N2-[2-Piperidino-5-(trifluoromethyl)phenyl]-3-chlorobenzo[b]-thiophene-2-carboxamide;

(xxxvi) 1-[2-(1-Naphthyloxy)ethoxy]naphthalene;

(xxxvii) 1,2-Di[3,5-di(trifluoromethyl)phenyl]hydrazine;

(xxxviii) 1-{2-[(4-Chlorobenzyl)thio]phenyl}-1H-pyrrole;

(xxxix) 1-[2,6-Dinitro-4-(trifluoromethyl)phenyl]-4-(3-{1-[2,6-dinitro-4-(trifluoro methyl)phenyl]-4-piperidyl}propyl)piperidine;

(xli) 2-[4-(4-Chlorophenyl)-1,3-thiazol-2-yl]-3-(dimethylamino)-acrylonitrile;

(xlii) 1-[5-(3,4-Dichlorophenyl)-2-furyl]ethan-1-one;

(xliii) 2,5-Di(1-naphthylmethylidene)cyclopentan-1-one;

(xliv) 5-(2-Thienyl)tetrahydrothiophen-3-one;

(xlv) 7-Nitro-1H-indole-2-carboxylic acid;

(xlvi) N",N"'-Di(5-chloro-2-hydroxybenzylidene)carbonic dihydrazide;

(xlvii) 2-(3-Nitrophenyl)-6-phenyl-4-(2-thienyl)pyridine;

(xlviii) 2-{[4-Chloro-2-nitro-5-(1H-pyrrol-1-yl)phenyl]thio}-4,5-diphenyl-1,3-oxazole;

(xlix) 2,5-Bis(2-thienyl)thiophene;

(l) N-(3,5-Dichlorophenyl)-4-(2'-fluoro[1,1'-biphenyl]-4-yl)-5-methyl-1,3-thiazol-2-amine;

(li) N-[1-[3,5-Bis(trifluoromethyl)phenyl]-3-(2-furyl)-1H-pyrazol-5-yl]-5-(4-chlorophenyl)-2-methyl-3-furamide;

(lii) 2-[(5-Nitro-1,3-thiazol-2-yl)thio]aniline;

(liii) 5-(Prop-2-ynylthio)-1,3,4-thiadiazole-2-thiol;

(liv) 4-oxo-2-phenyl-3,4-dihydroquinazolin-3-yl 3-(2,6-dichlorophenyl)-5-methylisoxazole-4-carboxylate;

(lv) 2-(2-chlorophenyl)-4H-3,1-benzoxazin-4-one;

(lvi) 2-[4-(tert-butyl)phenyl]-6,8-dichloro-4H-3,1-benzoxazin-4-one;

(lvii) 6,8-dimethyl-2-[4-(trifluoromethyl)phenyl]-4H-3,1-benzoxazin-4-one;

(lviii) 2-{2-[(2,4-dichlorophenoxy)methyl]-4-oxo-3,4-dihydroquinazolin-3-yl}-4-nitroisoindoline-1,3-dione;

(lix) 2-[4-(tert-butyl)phenyl]-6,8-dimethyl-4H-3,1-benzoxazin-4-one;

(lx) 2-phenyl-4H-3,1-benzoxazin-4-one;

(lxi) 2-[4-(tert-butyl)phenyl]-5-fluoro-4H-3,1-benzoxazin-4-one;

(lxii) 4-(2'-fluoro[1,1'-biphenyl]-4-yl)-5-methyl-2-(3-thienyl)-1,3-thiazole;

(lxiii) 2-(2-thienyl)-4H-3,1-benzoxazin-4-one;

(lxiv) 4,4'-bis[2-nitro-4-(trifluoromethyl)phenoxy]-1,1'-biphenyl;

(lxv) N1-[2-(4-chloro-3,5-dimethylphenoxy)-5-(trifluoromethyl)phenyl]-3,5-di(trifluoromethyl)benzene-1-sulfonamide;

(lxvi) N1-[3,5-di(trifluoromethyl)phenyl]-3,5-di(trifluoromethyl)benzene-1-sulfonamide;

(lxvii) 4'-{[(3,4-dichlorophenyl)sulfonyl]oxy}[1,1'-biphenyl]-4-yl 3,4-dichlorobenzenesulfonate;

(lxviii) 6,8-dibromo-2-(4-nitrophenyl)-4H-3,1-benzoxazin-4-one;

(lxix) 6,8-dibromo-5-fluoro-2-[3-(trifluoromethyl)phenyl]-4H-3,1-benzoxazin-4-one;

(lxx) 6,8-dibromo-5-fluoro-2-(2-thienyl)-4H-3,1-benzoxazin-4-one;

(lxxi) 2-bromo-6-nitro-4-(trifluoromethyl)phenyl 4'-propyl[1,1'-biphenyl]-4-carboxylate;

(lxxii) N-[2,6-bis(phenylthio)pyridin-3-yl]-N'-(3-chlorophenyl)urea;

(lxxiii) 2'-fluoro-N-(4-methoxyphenyl)[1,1'-biphenyl]-4-carboxamide;

(lxxiv) 2-(4-chlorophenyl)-4-(2'-fluoro[1,1'-biphenyl]-4-yl)-5-methyl-1,3-thiazole;

(lxxv) N-(3,5-dichlorophenyl)-4-(2'-fluoro[1,1'-biphenyl]-4-yl)-5-methyl-1,3-thiazol-2-amine;

(lxxvi) 6,8-dibromo-3-(4-fluorophenyl)-2-methyl-3,4-dihydroquinazolin-4-one;

(lxxvii) 7-chloro-2-(2-thienyl)-4H-3,1-benzoxazin-4-one;

(lxxviii) 5-fluoro-2-[3-(trifluoromethyl)phenyl]-4H-3,1-benzoxazin-4-one;

(lxxix) N-[2,6-bis(phenylthio)pyridin-3-yl]-N'-(3-chloro-4-fluorophenyl)-urea;

(lxxx) 3,3'-dinitro[1,1'-biphenyl]-4,4'-diamine;

(lxxxi) 2-(5-methyl-2-nitrophenyl)-4H-3,1-benzoxazin-4-one;

(lxxxii) 2-(2,4-dichlorophenyl)-6-iodo-4H-3,1-benzoxazin-4-one;

(lxxxiii) 8-bromo-6-methyl-2-[3-(trifluoromethyl)phenyl]-4H-3,1-benzoxazin-4-one;

(lxxxiv) 6-bromo-2-methyl-3-(4-methylphenyl)-3,4-dihydroquinazolin-4-one;

(lxxxv) 2-(3-chlorophenyl)-4H-3,1-benzoxazin-4-one;

(lxxxvi) N-[2,6-bis(phenylthio)pyridin-3-yl]-N'-(3-nitrophenyl)urea;

(lxxxvii) 7-chloro-2-(3-methylphenyl)-4H-3,1-benzoxazin-4-one;

(lxxxviii) 4'-({[3-(2,6-dichlorophenyl)-5-methylisoxazol-4-yl]carbonyl}-oxy)[1,1'-biphenyl]-4-yl 3-(2,6-dichlorophenyl)-5-methyl-isoxazole-4-carboxylate;

(lxxxix) N1-{4-[3,5-di(trifluoromethyl)phenoxy]phenyl}-3,5-di(trifluoro-methyl)benzene-1-sulfonamide;

(xc) N1-[2-fluoro-5-(trifluoromethyl)phenyl]-3,5-di(trifluoromethyl)-benzene-1-sulfonamide;

(xci) N1-(2,4-difluorophenyl)-3,5-di(trifluoromethyl)benzene-1-sulfonamide;

(xcii) 2-[3-(2,6-dichlorophenyl)-5-methylisoxazol-4-yl]-5-fluoro-4H-3,1-benzoxazin-4-one;

(xciii) N1-[2-({[3,5-di(trifluoromethyl)phenyl]sulfonyl}amino)phenyl]-3,5-di(trifluoromethyl)benzene-1-sulfonamide;

(xciv) 2-(4-chlorophenyl)-5-[2-(4-chlorophenyl)-1H-benzo[d]imidazol-6-yl]-1H-benzo[d]imidazole;

(xcv) 4'-ethyl[1,1'-biphenyl]-4-yl 2-bromo-6-nitro-4-(trifluoromethyl)-benzoate;

(xcvi) 4-(tert-butyl)phenyl 4-(2-chloro-6-nitrophenoxy)benzene-1-sulfonate;

(xcvii) 2'-fluoro[1,1'-biphenyl]-4-carboxylic acid;

(xcviii) [1,1'-biphenyl]-4-yl(5-nitro-1-benzofuran-2-yl)methanone;

(xcix) 1-(2'-fluoro[1,1'-biphenyl]-4-yl)propan-1-one N-(4-nitrophenyl)-hydrazone;

(c) 2-(2,4-dichlorophenyl)-6-nitro-4H-3,1-benzoxazin-4-one;

(ci) N-[2,6-bis(phenylthio)pyridin-3-yl]-N'-[4-(trifluoromethoxy)-phenyl]urea;

(cii) 6,8-dibromo-2-phenyl-4H-3,1-benzoxazin-4-one;

(ciii) 2-(2-chloro-6-fluorophenyl)-5-fluoro-4H-3,1-benzoxazin-4-one;

(ciiv) 6-methyl-2-(5-nitro-2-furyl)-4H-3,1-benzoxazin-4-one;

(cv) 2-[4-(tert-butyl)phenyl]-7-chloro-4H-3,1-benzoxazin-4-one;

(cvi) N1-[2,4-dichloro-5-(trifluoromethyl)phenyl]-3,5-di(trifluoromethyl)benzene-1-sulfonamide;

(cvii) 6,8-dichloro-2-[3-(trifluoromethyl)phenyl]-4H-3,1-benzoxazin-4-one;

(cviii) 3-bromo-2-methoxy-5-phenyl-1,1'-biphenyl;

(cix) 6,8-dibromo-5-chloro-2-[3-(trifluoromethyl)phenyl]-4H-3,1-benzoxazin-4-one;

(cx) 2-[2-nitro-4-(trifluoromethyl)phenoxy]phenyl benzo[b]thiophene-2-carboxylate;

(cxi) 4,4'-bis[(3,4-dichlorophenyl)sulfonyl]-1,1'-biphenyl;

(cxii) 3-chloro-N'-(3-chlorobenzoyl)benzohydrazide;

(cxiii) N-(4-[1,1'-biphenyl]-4-yl-1,3-thiazol-2-yl)-5-chloro-2-hydroxy-benzamide;

(cxiv) 6-bromo-3-(3,4-dichlorophenyl)-2-methyl-3,4-dihydroquinazolin-4-one;

(cxv) 2-nitro-1-[4-({4-[2-nitro-4-(trifluoromethyl)phenoxy]phenyl}-sulfonyl)phenoxy]-4-(trifluoromethyl)benzene;

(cxvi) 3-nitro-2-({4'-[(3-nitropyridin-2-yl)oxy][1,1'-biphenyl]-4-yl}oxy)-pyridine;

(cxvii) 2-(2-chlorophenyl)-6-iodo-4H-3,1-benzoxazin-4-one;

(cxviii) 7-chloro-2-(5-methyl-3-phenylisoxazol-4-yl)-4H-3,1-benzoxazin-4-one;

(cxix) 5-nitro-2-({4'-[(5-nitropyridin-2-yl)oxy][1,1'-biphenyl]-4-yl}oxy)-pyridine;

(cxx) 4,4'-dimethyl-3,3'-dinitro-1,1'-biphenyl;

(cxxi) 2-(2-furyl)-4H-3,1-benzoxazin-4-one;

(cxxii) 4-(2'-fluoro[1,1'-biphenyl]-4-yl)-5-methyl-N-phenyl-1,3-thiazol-2-amine;

(cxxiii) 4'-[(2-chlorobenzoyl)oxy][1,1'-biphenyl]-4-yl 2-chlorobenzoate;

(cxxiv) 7-chloro-2-(3-chlorobenzo[b]thiophen-2-yl)-4H-3,1-benzoxazin-4-one;

(cxxv) 4-[2-nitro-4-(trifluoromethyl)phenoxy]-1,1'-biphenyl;

(cxxvi) 2-{4-[2-nitro-4-(trifluoromethyl)phenoxy]phenyl}-3-[4-(trifluoromethyl)phenyl]acrylonitrile;

(cxxvii) N-(4-chlorophenyl)-N'-{6-[4-(trifluoromethyl)piperidino]-3-pyridyl}urea;

(cxxviii) 3,3'-dichloro-4,4'-dimethyl-1,1'-biphenyl;

(cxxix) 5-fluoro-2-(2-oxo-2H-chromen-3-yl)-4H-3,1-benzoxazin-4-one;

(cxxx) 2-(2'-fluoro[1,1'-biphenyl]-4-yl)-5-methoxy-3-methyl-1H-indole;

(cxxxi) methyl 3-[2-({[3,5-bis(trifluoromethyl)phenyl]sulfonyl}amino)-4-(trifluoromethyl)phenoxy]thiophene-2-carboxylate;

(cxxxii) 2-(3-chlorobenzo[b]thiophen-2-yl)-4H-3,1-benzoxazin-4-one;

(cxxxiii) 6-chloro-2-(5-nitro-2-thienyl)quinazolin-4(1H)-one;

(cxxxiv) 2-[2-(2-furyl)vinyl]-6-methyl-4H-3,1-benzoxazin-4-one;

(cxxxv) 5-[4-(2'-fluoro[1,1'-biphenyl]-4-yl)-5-methyl-1,3-thiazol-2-yl]-4-methyl-1,2,3-thiadiazole;

(cxxxvi) 5-[(4-chlorophenyl)sulfonyl]-2-nitrophenyl benzo[b]thiophene-2-carboxylate;

(cxxxvii) 2-nitro-4-(trifluoromethyl)phenyl 4'-propyl[1,1'-biphenyl]-4-carboxylate;

(cxxxviii) 1-[4-(benzyloxy)phenoxy]-2-nitro-4-(trifluoromethyl)benzene;

(cxxxix) 2-[2-(4-methoxyphenoxy)-5-nitrophenyl]-5-methyl-4H-3,1-benzoxazin-4-one;

(cxl) 5-(2-fluorophenyl)-3-{4-[2-nitro-4-(trifluoromethyl)phenoxy]-phenyl}-1,2,4-oxadiazole;

(cxli) 3-nitro-7H-benzo[de]anthracen-7-one;

(cxlii) 4-(cyanomethyl)phenyl 3-chlorobenzo[b]thiophene-2-carboxylate;

(cxliii) N1-[2-(4-oxo-4H-3,1-benzoxazin-2-yl)phenyl]-4-chlorobenzene-1-sulfonamide;

(cxliv) 1,1'-bis(4-chlorobenzoate) bi-2-naphthyl;

(cxlv) 2-[3-(2-chlorophenyl)-5-methylisoxazol-4-yl]-6-iodo-4H-3,1-benzoxazin-4-one;

(cxlvi) 1-bromo-5-(tert-butyl)-3-chloro-2-[2-nitro-4-(trifluoromethyl)-phenoxy]benzene;

(cxlvii) 2-(tert-butyl)-1,4-di[2-nitro-4-(trifluoromethyl)phenoxy]benzene;

(cxlviii) 4-chlorophenyl 4-(2-chloro-6-nitrophenoxy)benzene-1-sulfonate;

(cxlix) N'1-(3-chlorobenzoyl)-3-nitrobenzene-1-carbohydrazide;

(cl) 4-(6-chloro-1-methyl-4-oxo-1,4-dihydroquinazolin-2-yl)benzo-nitrile;

(cli) N-phenyl-N'-{6-[4-(trifluoromethyl)piperidino]-3-pyridyl}urea;

(clii) 4'-ethyl-N-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl][1,1'-biphenyl]-4-carboxamide;

(cliii) 6,8-dibromo-2-methyl-3-[3-(trifluoromethyl)phenyl]-3,4-dihydro-quinazolin-4-one;

(cliv) 2'-fluoro-N-[4-(trifluoromethyl)phenyl][1,1'-biphenyl]-4-carboxamide;

(clv) 2-[2-nitro-4-(trifluoromethyl)phenoxy]phenyl 3-(2-chloro-6-fluoro-phenyl)-5-methylisoxazole-4-carboxylate;

(clvi) 1-(4-ethyl-3-methylphenoxy)-2-nitro-4-(trifluoromethyl)benzene;

(clvii) N'1-[4-(tert-butyl)benzoyl]-4-(tert-butyl)benzene-1-carbohydrazide;

(clviii) N'1-(4-chlorobenzoyl)-3,5-di(trifluoromethyl)benzene-1-carbo-hydrazide;

(clix) 4-iodo-4'-nitro-1,1'-biphenyl;

(clx) 2'-fluoro-N-[3-(trifluoromethyl)phenyl][1,1'-biphenyl]-4-carboxamide;

(clxi) 2-(4-cyclohexylphenoxy)-1,3-dinitro-5-(trifluoromethyl)benzene;

(clxii) 2-styryl-4H-3,1-benzoxazin-4-one;

(clxiii) ethyl 1-[4-({[3,5-di(trifluoromethyl)phenyl]sulfonyl}amino)-phenyl]-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate;

(clxiv) 2-chloro-4-fluorophenyl 3-chlorobenzo[b]thiophene-2-carboxylate;

(clxv) 2-[2-(2-furyl)vinyl]-4H-3,1-benzoxazin-4-one;

(clxvi) 2-(2,6-difluorophenyl)-4-oxo-4H-3,1-benzoxazin-6-yl thiocyanate;

(clxvii) 2-(5-nitro-2-furyl)-4H-3,1-benzoxazin-4-one;

(clxviii) N1-(4-methoxy-2-nitrophenyl)-3,5-di(trifluoromethyl)benzene-1-sulfonamide;

(clxix) N-(3,5-dichlorophenyl)-N'-{2-[4-(trifluoromethyl)piperidino]-3-pyridyl}urea;

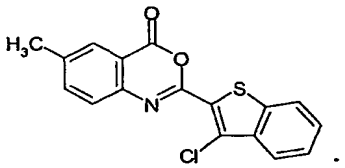
(clxx) 2-chloro-1,3-dimethyl-5-[2-nitro-4-(trifluoromethyl)phenoxy]-benzene;

(clxxi) 3-(3-{4-[2-nitro-4-(trifluoromethyl)phenoxy]phenyl}-1,2,4-oxadiazol-5-yl)-2H-chromen-2-one;

(clxxii) 1,4-di(tert-butyl)-2,5-di[2-nitro-4-(trifluoromethyl)phenoxy]-benzene;

(clxxiii) N-[1,1'-biphenyl]-4-yl-1-{2-[(2-chloro-6-fluorobenzyl)thio]ethyl}-2-methyl-5-phenyl-1H-pyrrole-3-carboxamide;

(clxxiv)



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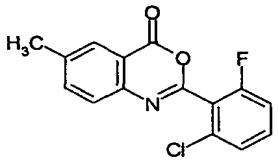

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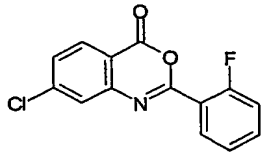

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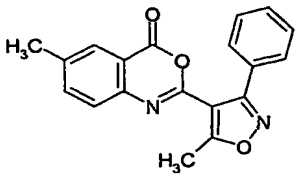

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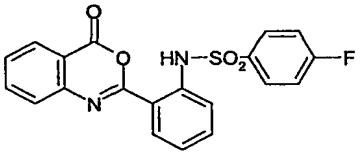

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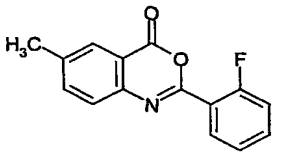

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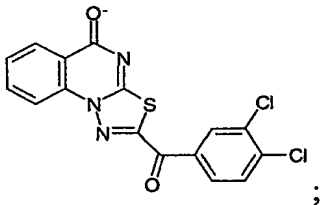

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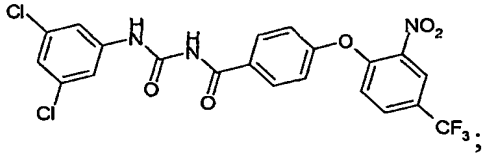

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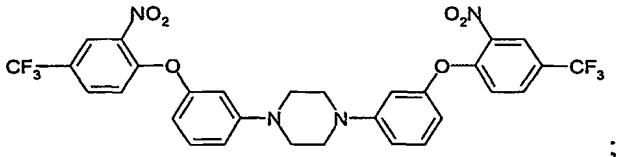

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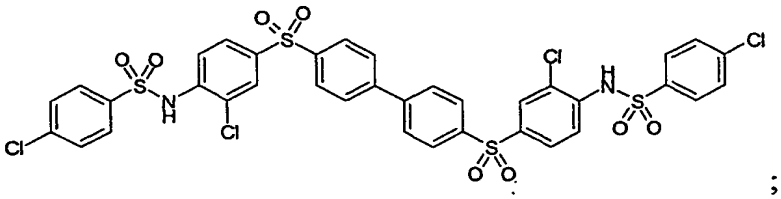

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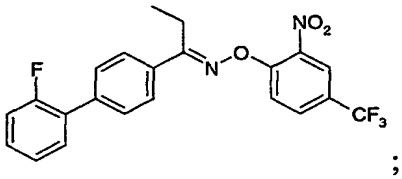

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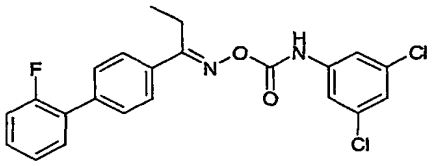

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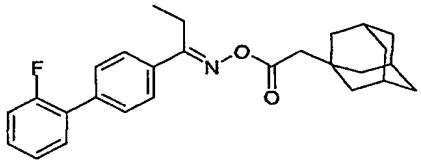

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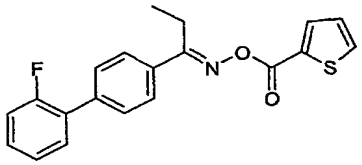

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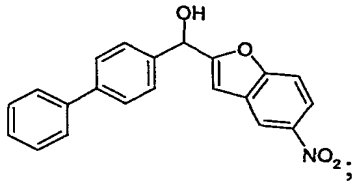
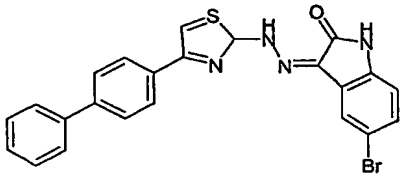


(clxxxix)



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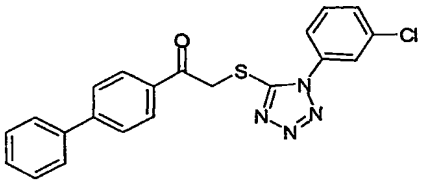
(cxc)



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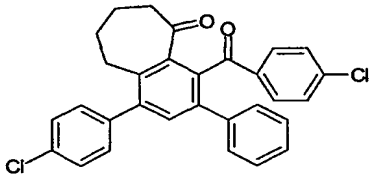
(cxci)



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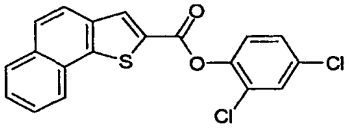
(cxcii)



for the preparation of a medicament for the treatment of cancer.

51. A compound as defined in any one of Claims 1 to 50 for use in medicine.

52. A pharmaceutical composition comprising a compound as defined in any one of Claims 1 to 50 and a pharmaceutically acceptable carrier.

53. The use of a compound as defined in Claim 50 as a lead compound in the identification of a low molecular weight AP endonuclease inhibitor.

54. Use as claimed in Claim 53, wherein the AP endonuclease inhibitor is mammalian.

55. Use as claimed in Claim 54, wherein the AP endonuclease inhibitor is HAP1.

56. Use as claimed in any one of Claims 1 to 4 or 50, wherein the medicament is prepared for treatment of cancer in a patient who is administered a DNA damaging agent.

57. Use as claimed in Claim 56, wherein the DNA damaging agent is administered prior to, during and/or following treatment of the patient with the medicament that is prepared using a low molecular weight mammalian AP endonuclease inhibitor.

58. Use as claimed in any one of Claims 5 to 49, wherein the medicament is prepared for the treatment of cancer in a patient who is administered a DNA damaging agent.

59. Use as claimed in Claim 58, wherein the DNA damaging agent is administered prior to, during and/or following treatment of the patient with the medicament that is prepared using a compound of formula I, Ia, Ib, IIa, IIb, III, IV or V, as defined in any one of Claims 5 to 49.

60. Use as claimed in any one of Claims 56 to 59, wherein the DNA damaging agent is an agent that induces the production of an AP site in DNA.

61. Use as claimed in any one of Claims 1 to 4 or 50, wherein the medicament is prepared from a combination of a chemical DNA damaging agent and a low molecular weight mammalian AP endonuclease inhibitor.

62. Use as claimed in any one of Claims 5 to 49, wherein the medicament is prepared from a combination of a chemical DNA damaging agent and a compound of formula I, Ia, Ib, IIa, IIb, III, IV or V, as defined in any one of Claims 5 to 49.

63. A method for treating cancer, which method comprises the administration of a low molecular weight mammalian AP endonuclease inhibitor, as defined in any one of Claims 1 to 4 or 50, to a patient in need of cancer treatment.

64. A method for treating cancer, which method comprises the administration of a compound of formula I, Ia, Ib, IIa, IIb, III, IV or V, as defined in any one of Claims 5 to 49, to a patient in need of cancer treatment.

65. A method as claimed in Claim 63, which method comprises administration of the low molecular weight mammalian AP endonuclease inhibitor in combination with a DNA damaging agent.

66. A method as claimed in Claim 65, which method comprises administration of the DNA damaging agent before, at the same time as, and/or after administration of the low molecular weight mammalian AP endonuclease inhibitor.

67. A method as claimed in Claim 64, which method comprises administration of the compound of formula I, Ia, Ib, IIa, IIb, III, IV or V in combination with a DNA damaging agent.

68. A method as claimed in Claim 67, which method comprises administration of the DNA damaging agent before, at the same time as, and/or after administration of the compound of formula I, Ia, Ib, IIa, IIb, III, IV or V.

69. A method as claimed in any one of Claims 65 to 68, wherein the DNA damaging agent is an agent that induces the production of an AP site in DNA.

70. A method as claimed in any one of Claims 63, 65 and 66, which method comprises administering a reduced dose of DNA damaging agent in combination with a low molecular weight mammalian AP endonuclease inhibitor to a patient in need of cancer treatment.

71. A composition comprising:

(a) a chemotherapeutic agent; and

(b) a low molecular weight mammalian AP endonuclease inhibitor, as defined in any one of Claims 1 to 4 or 50.

72. A composition comprising:

(a) a chemotherapeutic agent; and

(b) a compound of formula I, Ia, Ib, IIa, IIb, III, IV or V, as defined in any one of Claims 5 to 49.

73. A composition as claimed in Claim 71 or Claim 72, wherein the chemotherapeutic agent is a chemical DNA damaging agent.

74. A composition as claimed in any one of Claims 71 to 73 for use in medicine.

75. A pharmaceutical composition comprising:

(a) a chemotherapeutic agent;

(b) a low molecular weight mammalian AP endonuclease inhibitor, as defined in any one of Claims 1 to 4 or 50; and

(c) a pharmaceutically acceptable carrier.

76. A pharmaceutical composition comprising:

(a) a chemotherapeutic agent;

(b) a compound of formula I, Ia, Ib, IIa, IIb, III, IV or V, as defined in any one of Claims 5 to 49; and

(c) a pharmaceutically acceptable carrier.

77. A composition as claimed in Claim 75 or Claim 76, wherein the chemotherapeutic agent is a chemical DNA damaging agent.

78. A therapeutic system comprising:

(a) a chemotherapeutic agent; and

(b) a low molecular weight mammalian AP endonuclease inhibitor, as defined in any one of Claims 1 to 4 or 50.

79. A therapeutic system comprising:

(a) a chemotherapeutic agent; and

(b) a compound of formula I, Ia, Ib, IIa, IIb, III, IV or V, as defined in any one of Claims 5 to 49.

80. A therapeutic system as claimed in Claim 78 or Claim 79, wherein the chemotherapeutic agent is a chemical DNA damaging agent.

81. The use of a low molecular weight mammalian AP endonuclease inhibitor, as defined in any one of Claims 1 to 4 or 50, for the preparation of a medicament for the treatment of a condition where inhibition of a mammalian AP endonuclease is required or desired.

82. Use as claimed in Claim 81, wherein the condition is a chronic inflammatory or oxyradical overload disease.

83. Use as claimed in Claim 82, wherein the condition is ulcerative colitis, viral hepatitis, Wilson disease, haemochromatosis, chronic gastritis, chronic pancreatitis or Barret oesophagus.

84. Use as claimed in Claim 81, wherein the condition is Alzheimer's disease.

85. A method of inhibiting a mammalian AP endonuclease, which method comprises administering a low molecular weight mammalian AP endonuclease inhibitor, as defined in any one of Claims 1 to 4 or 50.

86. A method as claimed in Claim 85, wherein the low molecular weight mammalian AP endonuclease inhibitor is administered to a patient who has a condition where inhibition of a mammalian AP endonuclease is required or desired.

87. The use of a compound of formula I, Ia, Ib, IIa, IIb, III, IV or V, as defined in any one of Claims 5 to 49 for the preparation of a medicament for the treatment of a microbial disease.

88. A method of detecting the mutagenic, cytotstatic or cytotoxic nature of a test compound, which method comprises:

(i) preparing test cells by contacting cells with one or more mammalian AP endonuclease inhibitors, as defined in any one of Claims 1 to 4 or 50; and

(ii) in those test cells, monitoring the frequency of phenotypic change, the cell proliferation or the frequency of cell death (as appropriate) in the presence and absence of said test compound.

89. A method of preparing test cells suitable for detecting the mutagenic, cytotstatic or cytotoxic nature of a compound, which method comprises contacting cells with one or more mammalian AP endonuclease inhibitors, as defined in any one of Claims 1 to 4 or 50.

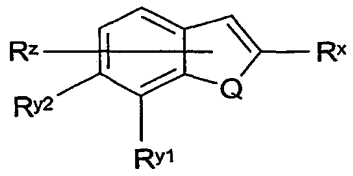
90. A method of assessing the ability of a test compound to protect against DNA damage, which method comprises:

(i) preparing test cells by contacting cells with one or more mammalian AP endonuclease inhibitors, as defined in any one of Claims 1 to 4 or 50;

(ii) contacting those test cells with a known carcinogen; and

(iii) monitoring the frequency of DNA damage in those test cells in the presence and absence of said test compound.

91. The use of a compound of formula VI,



VI

wherein Q represents O, S or NH;

R^x represents $C(O)OR^{xa}$ or $C(O)N(R^{xb})R^{xc}$;

R^{y1} represents a substituent selected from halo, nitro and C_{1-6} alkyl, or R^{y1} and R^{y2} together form a fused benzene ring that is optionally substituted by R^z;

R^{y2} is absent or R^{y2} and R^{y1} together form a fused benzene ring that is optionally substituted by R^z;

R^z represents one or more optional substituents selected from halo, nitro, C_{1-6} alkyl and C_{1-6} alkoxy;

R^{xa} represents H, C_{1-6} alkyl, aryl or Het^{xa};

R^{xb} represents H, C_{1-6} alkyl, aryl or Het^{xb};

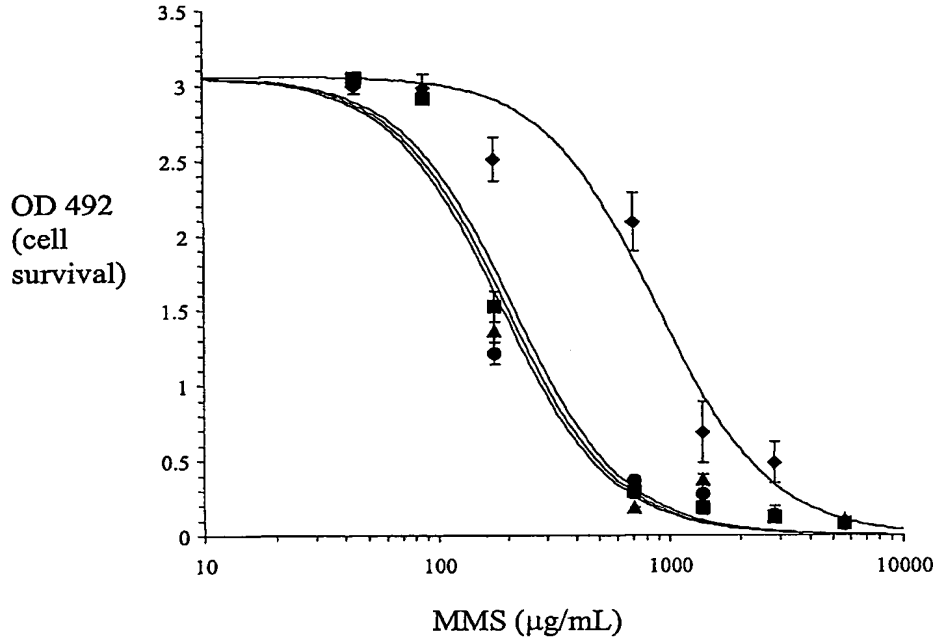
R^{xc} represents H or C_{1-6} alkyl;

Het^{xa} and Het^{xb} independently represent four- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from N, O and S, which heterocyclic groups are optionally substituted by one or more substituents selected from =O, OH, halo, nitro, cyano, C_{1-6} alkyl, aryl and NH_2;

wherein each aryl group, unless otherwise specified, is optionally substituted;

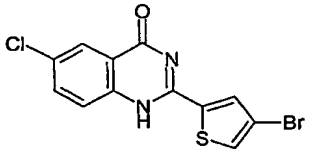
for the preparation of a medicament for the treatment of cancer.

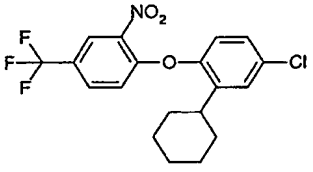
Figure 1



Key

◆ : No inhibitor

▲ :  (Formula IIa) at 100 μM

● :  (Formula Ia) at 100 μM

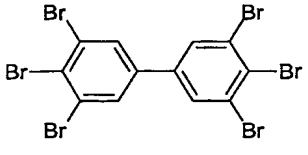
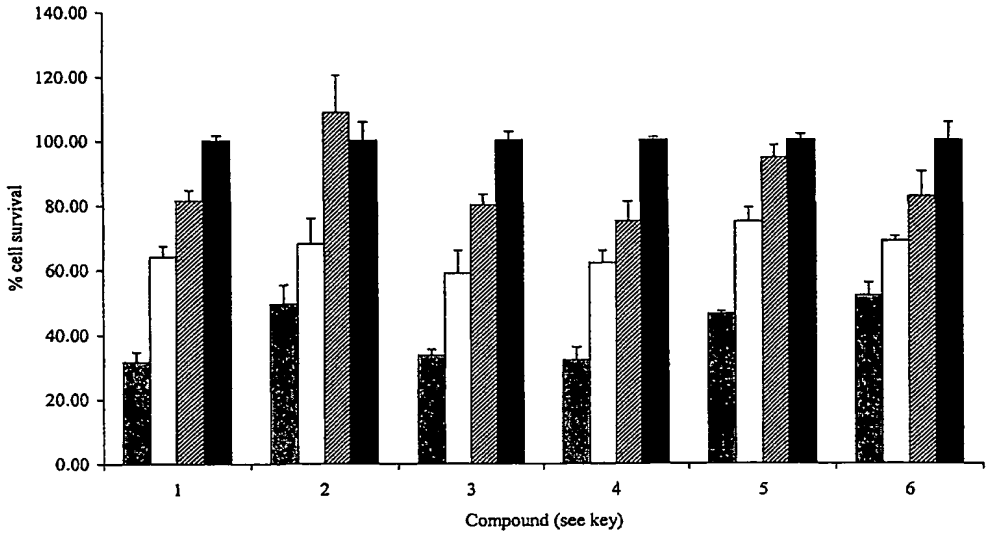
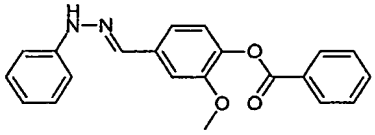
■ :  (Formula Ia) at 100 μM

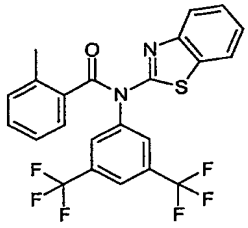
Figure 2



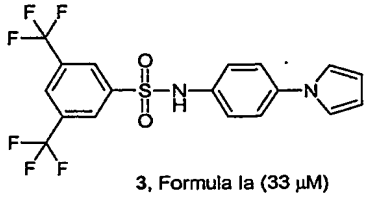
Key



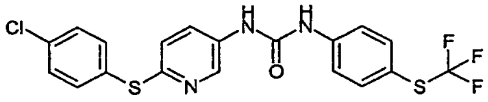
1, Formula Ia (100 µM)



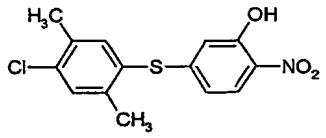
2, Formula Ia (33 µM)



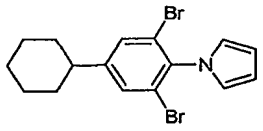
3, Formula Ia (33 µM)



4, Formula Ib (17 µM)



5, Formula Ia (100 µM)



6, Formula Ib (33 µM)

Solid black bars – Cells only. Hatched bars – Cells plus compound only. Open bars – Cells plus MMS only. Solid grey bars – cells plus compounds and MMS.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(25) Filing Language: English

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(71) Applicant *(for all designated States except US)*: **CANCER RESEARCH TECHNOLOGY LIMITED** [GB/GB]; 61 Lincoln's Inn Fields, London WC2A 3PX (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HICKSON, Ian , David** [GB/GB]; Molecular Oncology-Genome Integrity Group, Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford OX3 9DS (GB). **HAMMONDS, Timothy, Robin** [GB/GB]; Applied Development Laboratory, Dominion House, 59 Bartholomew Close, London EC1A 7BE (GB).

(74) Agent: **MILES, John, S.**; Eric Potter Clarkson, Park View House, 58 The Ropewalk, Nottingham NG1 5DD (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
1 May 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/007955 A3

(54) Title: BIPHENYL APURINIC/APYRIMIDINIC SITE ENDONUCLEASE INHIBITORS TO TREAT CANCER

(57) Abstract: The present invention provides the use of a low molecular weight mammalian AP endonuclease inhibitor for the preparation of a medicament for the treatment of cancer.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 02/03342

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4545 A61K31/085 A61K31/27 A61K31/255 A61K31/265
A61P35/00 A61K31/26 A61K31/655 A61K31/235 A61K31/517
A61K31/536 A61K31/343 A61K31/428 A61K31/385 A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 703 130 A (GUO ZONG-RU ET AL) 30 December 1997 (1997-12-30) column 4, line 1 ---	1-37, 50-52, 56-80
X	US 6 190 661 B1 (DUQUID JOHN ET AL) 20 February 2001 (2001-02-20) cited in the application claims 4,5 ---	1-4,51, 52,56-80
X	EP 0 639 567 A (OTSUKA PHARMA CO LTD) 22 February 1995 (1995-02-22) page 5, line 2 - line 5 page 99; example 279	1-36, 50-52, 56-80
X	page 31 -page 32 page 112; table 21 --- -/--	38

[X] Further documents are listed in the continuation of box C.

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 February 2003	07. 03. 03

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Trifilieff-Riolo, S

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INTERNATIONAL SEARCH REPORT

Intern! ıl Application No
PCT/GB 02/03342

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4025 A61K31/44 A61K31/381 A61K31/47 A61K31/404

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STEVENS ET AL.: "Antitumor activity, biomimetic oxidation and metabolism of heteroalicyclic triazenes" BIOCHEM. PHARMACOL., vol. 28, no. 6, 1979, pages 769-776, XP008012827 page 770 page 771; table 1 page 774, right-hand column ---	1-4,39, 43,51, 52,63,64
X	HADFIELD ET AL.: "Structure-activity studies on 2-aryl-4H-3,1-benzoxazin-4-ones" ANTI-CANCER DRUGS, vol. 5, no. 5, 1994, pages 533-538, XP008012811 page 534; figure 1 page 535; table 1 ---	1-4,39, 43-52, 56-80

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 February 2003	07. 03. 03

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Trifilieff-Riolo, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 02/03342

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 239 130 B1 (BURNOUF CATHERINE ET AL) 29 May 2001 (2001-05-29) examples 1-36 column 48, line 15 - line 25	51,52, 71,72, 74-76, 78,79
X	WO 99 48878 A (NOVONORDISK AS) 30 September 1999 (1999-09-30) examples 1-8	51,52
X	WO 99 08501 A (REDDY RESEARCH FOUNDATION ;REDDY CHEMINOR INC (US)) 25 February 1999 (1999-02-25) examples 49,50,58	51,52
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X,P	US 6 337 332 B1 (CARPINO PHILIP A) 8 January 2002 (2002-01-08) example 1A; table 1 example 2A; table 2	51,52
X	WO 99 32106 A (BAYER AG) 1 July 1999 (1999-07-01) page 80 -page 111	1-36,38, 50-52, 56-80

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INTERNATIONAL SEARCH REPORT

Interr I Application No
PCT/GB 02/03342

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 093 742 A (SALITURO FRANCESCO GERALD ET AL) 25 July 2000 (2000-07-25) compounds 18,42,43,56,72 to 75,80 to 82,85,86,101 to 103,126,129 to 139 claim 15	1-36,38, 50-52, 56-80
X	US 5 464 861 A (DOBRUSIN ELLEN M ET AL) 7 November 1995 (1995-11-07) column 19; examples 22,23	1-36,38, 50-52, 56-80
X	WO 99 32436 A (BAYER AG) 1 July 1999 (1999-07-01) examples 61,63-69,94-96	1-36,38, 50-52, 56-80
X	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 1982 POPOV D.: "Antitumor screening studies of oxazole derivatives" retrieved from STN CAPLUS Database accession no. 1982:15030 XP002230425 abstract & POPOV D.: "Antitumor screening studies of oxazole derivatives" PROBLEMI NA ONKOLOGIYATA, vol. 8, 1980, pages 59-62, abstract	1-36,38, 50-52, 56-80
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X	WO 97 49400 A (SMITHKLINE BEECHAM CORP ;WIDDOWSON KATHERINE L (US)) 31 December 1997 (1997-12-31) page 15	51,52

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 02/03342

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 63-70 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [X] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1-39,43-52,56-80 (all partially)

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 02 03342

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-39, 43-52, 56-80 relate to an extremely large number of possible compounds.
Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds which use is claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds prepared in the examples on pages 84 to 108 and closely related homologous compounds.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 02/03342

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-36 (partially), 37, 50-52 (partially), 56-80 (partially)

2. Claims: 1-36 (partially), 38, 50-52 (partially), 56-80 (partially)

3. Claims: 1-4 (partially), 39, 43-49, 50-52 (partially), 56-80 (partially)

4. Claims: 1-4 (partially), 40, 43-49, 50-52 (partially), 56-80 (partially)

5. Claims: 1-4 (partially), 41, 43-49, 50-52 (partially), 56-80 (partially)

6. Claims: 1-4 (partially), 42, 43-49, 50-52 (partially), 56-80 (partially)

7. Claims: 53-55

8. Claims: 81,85,86

9. Claims: 82,83

10. Claim : 84

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 02 03342

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

11. Claim : 87

12. Claims: 88-90

13. Claim : 91

INTERNATIONAL SEARCH REPORT

rmation on patent family members

Inter al Application No
PCT/GB 02/03342

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INTERNATIONAL SEARCH REPORT

rmation on patent family members

Inter il Application No
PCT/GB 02/03342

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